TOXICOLOGICAL PROFILE FOR 1,1,1-TRICHLOROETHANE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for 1,1,1-trichloroethane was released on December 1990. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, that describes in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on February 28, 1994 (59 FR 9486). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); and October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Foreword

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for 1,1,1-trichloroethane. The panel consisted of the following members:

1. Dr. James Bruckner, Professor and Director of Toxicology, University of Georgia, College of Pharmacology, Department of Pharmacology and Toxicology, Athens, GA;

2. Dr. Hugh Farber, Private Consultant, Midland, MI; and

3. Mr. Lyman Skory, Skory Consulting, Midland, MI.

These experts collectively have knowledge of 1,1,1-trichloroethane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about 1,1,1-trichloroethane and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,408 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. 1,1,1-Trichloroethane has been found in at least 696 of the sites on the NPL. However, the number of NPL sites evaluated for 1,1,1-trichloroethane is not known. As EPA evaluates more sites, the number of sites at which 1,1,1-trichloroethane is found may increase. This information is important because exposure to 1,1,1-trichloroethane may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,1,1-trichloroethane.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as 1,1,1-trichloroethane, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT IS 1,1,1-TRICHLOROETHANE?

1,1,1 -Trichloroethane is a synthetic chemical that does not occur naturally in the environment. It is also known as methylchloroform, methyltrichloromethane, trichloromethylmethane, and a-trichloromethane. Its registered trade names are chloroethene NU® and Aerothene TT®. It

is a colorless liquid with a sweet, sharp odor. 1,1,1 -Trichloroethane dissolves slightly in water. The liquid evaporates quickly and becomes a vapor in the air. Most people begin to smell 1,1,1-trichloroethane in the air when levels reach 120 to 500 parts of 1,1,1-trichloroethane per one million parts of air (ppm). If the chemical makes up 8 to 10.5% (80,000 to 105,000 ppm) of the air, 1,1,1-trichloroethane can bum easily when it comes in contact with a spark or flame. If the vapor bums at high temperatures such as those produced during welding operations, it can produce a poisonous gas known as phosgene. Because of its tendency to evaporate easily, the vapor form is most commonly found in the environment. 1,1,1-trichloroethane also can be found in soil and water, particularly at hazardous waste sites.

1,1,1 -Trichloroethane is used in commercial products, mostly to dissolve other chemicals. About 800 million pounds were produced in 1990, but less is being made today. By the year 1996, 1,1,1-trichloroethane will no longer be made in the United States because it affects the ozone layer. 1,1,1-Trichloroethane has many industrial and household uses. It is often used as a solvent to dissolve other substances, such as glues and paints. In industry, it is widely used to remove oil or grease from manufactured metal parts. In the home, it may be an ingredient of products such as spot cleaners, glues, and aerosol sprays.

You will find detailed information on the chemical properties of 1,1,1 -trichloroethane in Chapter 3. Chapter 4 describes production data and the uses of 1,1,1-trichloroethane.

1.2 WHAT HAPPENS TO 1,1,1-TRICHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

Most of the 1,1,1-trichloroethane released into the environment enters the air, where it lasts for about 6 years. Once in the air, it may travel to the upper part of the earth’s atmosphere, which is called the stratosphere. There, sunlight breaks it down into other chemicals that may reduce the stratospheric ozone layer. This ozone layer blocks certain damaging ultraviolet rays of the sun from reaching the earth’s surface. Some scientists think that the gradual

thinning of the ozone layer is causing increases in the number of skin cancer cases in humans.

Spills, improper disposal, industrial emissions, and consumer use can release large amounts of 1,1,1 -trichloroethane into the environment. Contaminated water from landfills and hazardous waste sites may contaminate surrounding soil and nearby surface water or groundwater. However, most of the chemical will probably eventually evaporate into the air. It will not build up in plants or animals. Industrial operations release the largest amount of 1,1,1-trichloroethane into the environment, mostly by emissions into the air. The vapor also enters the air because many products containing the chemical are used in the home and workplace.

We do not know how long 1,1,1-trichloroethane lasts in water or soil. In surface waters such as lakes and rivers, where it partially mixes with water, much of the chemical evaporates quickly into the air. 1,1,1-Trichloroethane also evaporates into the air from soil surfaces. Water can easily carry it through soil into groundwater. 1,1,1 -Trichloroethane in groundwater may evaporate and pass through soil as a gas and finally be released to the air. Also, organisms that live in soil and water may break down 1,1,1-trichloroethane. One study suggests that it takes 200 to 300 days for half of the chemical in contaminated groundwater to break down. However, the number of days may vary widely, depending on specific site conditions.

Chapter 5 provides further information on what happens to 1,1,1-trichloroethane in the environment.

1.3 HOW MIGHT I BE EXPOSED TO 1,1,1-TRICHLOROETHANE?

You can be exposed to 1,1,1-trichloroethane daily from a variety of sources. 1,1,1-Trichloroethane has been found in air samples taken from all over the world. In the United States, city air typically contains about 0.1 to 1.0 parts per billion (ppb) of 1,1,1-trichloroethane; rural air usually contains less than 0.1 ppb. Because 1,1,1-trichloroethane is used so frequently in

home and office products, much more is usually found in the air inside buildings (0.3 to 4.4 ppb) than in the outside air (0.1 to 0.9 ppb). Since this chemical is found in many building materials, new buildings can have higher indoor levels than old buildings. Thus, you are likely to be exposed to 1,1,1-trichloroethane vapor at higher levels indoors than outdoors or near hazardous waste sites.

Common consumer products that contain 1,1,1-trichloroethane include glues, household cleaners, and aerosol sprays. In the workplace, you may be exposed to 1,1,1-trichloroethane while using some metal degreasing agents, paints, glues, and cleaning products. You can be exposed to 1,1,1 -trichloroethane by breathing the vapors from these products or by letting the liquid come into contact with your skin. High levels of exposure have occurred in persons who deliberately inhaled the vapors, as in glue-sniffing or solvent abuse.

1,1,1-Trichloroethane has been found in rivers and lakes (up to 0.01 ppm), in soil (up to 120 ppm), in drinking water (up to 0.0035 ppm), and in drinking water from underground wells (up to 5.4 ppm). In one case, drinking water from a private well contained up to 12 ppm, possibly as a result of illegal discharge or spill from a nearby industrial plant. Releases during manufacture and transportation, and during industrial or household use can cause these high levels, but the levels vary substantially from one location to another. Certain foods you eat and water you drink or bathe in may be contaminated with 1,1,1-trichloroethane. However, you can be exposed to 1,1,1-trichloroethane primarily by drinking contaminated water and eating contaminated food. Chapter 5 discusses further information on human exposure to 1,1,1 -trichloroethane.

1.4 HOW CAN 1,1,1-TRICHLOROETHANE ENTER AND LEAVE MY BODY?

1,1,1-Trichloroethane can quickly enter your body if you breathe in air containing it in vapor form. It also enters your body if you drink water or eat food containing 1,1,1-trichloroethane. If you spill 1,1,1-trichloroethane on your skin, most of it quickly evaporates into the air, but small amounts enter your body through your skin. Regardless of how 1,1,1-trichloroethane enters your body, nearly all of it quickly leaves your body in the air you exhale. The small

amount that is not breathed out can be changed in your body into other substances, known as metabolites. Most of the metabolites leave your body in the urine and breath within a few days. Chapter 2 provides further information on how 1,1,1-trichloroethane can enter and. leave the body.

1.5 HOW CAN 1,1,1-TRICHLOROETHANE AFFECT MY HEALTH?

If you breathe air containing high levels of 1,1,1-trichloroethane (1,000 ppm or higher) for a short time you may become dizzy and lightheaded, and ,possibly lose your coordination. These effects will rapidly disappear after you stop breathing contaminated air. If you breathe in much higher levels of 1,1,1-trichloroethane, either intentionally or accidentally, you may become unconscious, your blood pressure may decrease, and your heart may stop beating. We do not know whether harmful effects result from breathing low levels of 1,1,1-trichloroethane for a long time. Studies in animals show that breathing air that contains very high levels of 1,1,1-trichloroethane (higher than 2,000 ppm) damages the breathing passages and causes mild effects in the liver, in addition to affecting the nervous system. We do not know if breathing air containing 1,1,1-trichloroethane affects reproduction or development in people. However, when rats were exposed to high levels of 1,1,1-trichloroethane in air, their offspring developed more slowly than normal. Similar exposure of pregnant rabbits delayed the setting of the bone structure of their offspring. These effects on the developing offspring of rats and rabbits were seen only at quite high levels that, in most cases, were toxic to the mother. There are no studies of people that tell us whether eating food or drinking water contaminated with 1,1,1-trichloroethane could cause harmful health effects. However, exposures to people who work with 1,1,1-trichloroethane do not usually cause harmful effects. In animals, placing large amounts of 1,1,1-trichloroethane in the animal’s stomach has caused effects on the nervous .system, mild liver damage, unconsciousness, and even death. If your skin comes into contact with 1,1,1-trichloroethane, you might feel some irritation. Studies in animals suggest that repeated exposure of the skin might affect the liver and that very large amounts on the skin can cause death. These effects only occurred when evaporation was prevented.

Available information does not indicate that 1,1,1-trichloroethane causes cancer. The International Agency for Research on Cancer (IARC) has determined that 1,1,1-trichloroethane is not classifiable as to its carcinogenicity in humans. The EPA has also determined that 1,1,1-trichloroethane is not classifiable as to its human carcinogenicity. The likelihood that exposure to levels of 1,1,1-trichloroethane found near hazardous waste sites would cause significant health effects is very low. You can find more information on the health effects of 1,1,1-trichloroethane in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,1,1-TRICHLOROETHANE?

Samples of your breath, blood, and urine can be tested to determine if you have recently been exposed to 1,1,1-trichloroethane. In some cases, these tests can estimate how much 1,1,1-trichloroethane has entered your body. To be of any value, samples of your breath or blood have to be taken within hours of exposure, and samples of urine have to be taken within 1 or 2 days after exposure. These tests will not tell you whether your health will be affected by exposure to 1,1,1-trichloroethane. The exposure tests are not routinely available in hospitals and clinics because they require special analytical equipment. See Chapters 2 and 6 for more information about tests for exposure to 1,1,1-trichloroethane.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The Environmental Protection Agency (EPA) sets regulations on the levels of 1,1,1-trichloroethane which are allowable in drinking water. The highest level of 1,1,1-trichloroethane allowed in drinking water is 0.2 ppm. The EPA has decided that the level of 1,1,1-trichloroethane in lakes and streams should not be more than 18 ppm. This level would prevent possible harmful health effects from drinking water and eating fish contaminated with 1,1,1-trichloroethane. Any releases or spills of 1,1,1-trichloroethane of 1,000 pounds or more must be reported to the National Response Center. 1,1,1-Trichloroethane levels in the workplace are regulated by the Occupational Safety and Health Administration (OSHA). The

workplace exposure limit for an 8-hour workday, 40-hour workweek is 350 ppm in air. See Chapter 7 for more information on regulations and advisories regarding 1,1,1-trichloroethane.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,1,1-trichloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,1,1-trichloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute-, intermediate-, and chronic-duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User’s Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.l Death

1,1,1-Trichloroethane is one of many solvents intentionally inhaled by some people to alter mood or consciousness. Solvent abuse of this type is associated with “sudden sniffing death” syndrome. In a survey of sudden sniffing deaths across the United States in the 1960s, 29 of the 110 deaths in the survey were attributed to inhalation of 1,1,1-trichloroethane (Bass 1970). Case reports of individuals who died following intentional inhalation of 1,1,1-trichloroethane are readily available (D’Costa and Gunasekera 1990; Droz et al. 1982; Guberan et al. 1976; Hall and Hine 1966; MacDougall et al. 1987; Ranson and Berry 1986; Travers 1974). 1,1,1-Trichloroethane is a widely used industrial solvent. Although mortality due to accidental exposure from its use as a solvent is not common, a number of cases have been reported (Caplan et al. 1976; Jones and Winter 1983; McCarthy and Jones 1983; Mercier 1977; Northfield 1981; Silverstein 1983; Stahl et al. 1969).

Data from case reports and surveys are useful, but concomitant exposure to other chemicals cannot be ruled out, and exposure concentrations and durations are rarely known. Although the actual levels of exposure that produced death are not known for any of these cases, some investigators used simulations to estimate the fatal exposure concentrations. Droz et al. (1982) performed detailed simulations of two fatalities from intentional 1,1,1-trichloroethane inhalation. The lethal concentration of 1,1,1-trichloroethane was estimated to be between 6,000 and 14,000 ppm in one case and between 10,000 and 20,000 ppm in the other. Simulation of the circumstances of deaths of two people exposed while using 1,1,1-trichloroethane as a solvent showed that concentrations 16,400 ppm may have been generated in one case (Jones and Winter 1983), and concentrations 19,000 ppm may have been generated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

Human death following acute exposure to high 1,1,1-trichloroethane concentrations is usually attributed to either depression of the central nervous system, which results in respiratory arrest (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969), or sensitization of the heart to epinephrine, which results in severe cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). The occurrence of death during physical exertion following inhalation of 1,1,1-trichloroethane

(Ranson and Berry 1986) or a mixture of 1,1,1-trichloroethane and trichloroethylene (King et al. 1985; Troutman 1988) is consistent with the possibility that cardiac sensitization to epinephrine caused death in these cases. It should be noted that anoxia or hypoxia, which are present to some extent during physical exertion, exacerbate the cardiac arrhythmias caused by sensitization of the myocardium to catecholamines (Reinhardt et al. 1971).

Studies of animal mortality following acute inhalation exposure to 1,1,1-trichloroethane are numerous. Median lethal concentrations (LC_{50} values) have been calculated for rats and mice. For rats, LC_{50} values from 10,305 to 38,000 ppm were reported (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982). For mice, reported LC_{50} values ranged from 3,911 to 22,241 ppm (Gradiski et al. 1978; Horiguchi and Horiguchi 1971; Moser and Balster 1985; Woolverton and Balster 1981). Much of the variation in these data can be attributed to differences in the exposure duration (higher LC_{50} values were generally obtained in studies with short exposure periods). In studies of the same duration, rats (6-hour LC_{50} = 10,305 ppm) were somewhat more susceptible to 1,1,1-trichloroethane than mice (6-hour LC_{50} = 13,414 ppm) (Bonnet et al. 1980; Gradiski et al. 1978). An alternative way to study lethality is to expose animals to a given concentration of vapor and record the time required to kill half of the animals (LT_{50}). The LT_{50} was 180 minutes in rats exposed to 18,000 ppm of 1,1,1-trichloroethane (Adams et al. 1950) and 595 minutes in mice exposed to 13,500 ppm (Gehring 1968). Deaths of animals exposed to 1,1,1-trichloroethane were usually attributed to either respiratory or cardiac failure (Adams et al. 1950; Clark and Tinston 1982; Krantz et al. 1959). Most deaths occurred during exposure. Animals that survived the exposure period usually recovered rapidly and appeared normal within 10-15 minutes (Adams et al. 1950; Clark and Tinston 1982).

1,1,1-Trichloroethane did not increase mortality in longer-term studies in which animals were exposed to lower exposure concentrations than the acute studies. No effects on survival were observed in intermediate-duration studies in which animals of several species were exposed to concentrations ≤5,000 ppm (Adams et al. 1950; Calhoun et al. 1981; Prendergast et al. 1967; Rosengren et al. 1985) or chronic-duration studies in which rats and mice were exposed to concentrations ≤1,750 ppm (Quast et al. 1978, 1988).

Reliable acute LC_{50} values for death in each species are recorded in Table 2-l and plotted in Figure 2-l. Acute exposure to high concentrations of 1,1,1-trichloroethane can be lethal to humans and animals. The cause of death is usually either respiratory or cardiac failure. Limited human data

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	1 d 6hr/d				10305 M (LC50 - 6 hr)	Bonnet et al. 1980
2	Rat (Alderley-Park)	1 d 10-15 min/d				38000 (LC50 - 15 min)	Clark and Tinston 1982
3	Rat (Wistar)	1 d 6-420 min/d				14250 (LC50 - 7 hr)	Adams et al. 1950
4	Mouse (OF1)	1 d 6hr/d				13414 F (LC50 - 6 hr)	Gradiski et al. 1978
5	Mouse (NA2)	1 d 2hr/d				3911 M (LC50 - 2 hr)	Horiguchi and Horiuchi 1971
6	Mouse (CD-1)	1 d 30 min/d				22241 M (LC50 - 30 min)	Woolverton and Balster 1981
7	Mouse (CD-1)	1 d 10-60 min/d				18358 M (LC50 - 60 min)	Moser and Balster 1985
	Systemic						
8	Human	1 d 30 min/d	Cardio	550 M			Gamberale and Hultengren 1973
9	Human	1 d 15-186 min/d	Resp		1900M (throat irritation)		Stewart et al. 1961
			Hepatic	2650 M			
			Renal	2650 M			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
10	Human	1 d up to 2 hr/d	Resp	10000			Dornette and Jones 1960
			Cardio		10000 (5-10 mm Hg reduction in blood pressure)		
			Hepatic	10000			
11	Human	5 d 1-7.5 hr/d	Resp	500			Stewart et al. 1975
			Hemato	500			
			Hepatic	500			
			Renal	500			
12	Human	1 d 5-450 min/d	Resp	506			Torkelson et al. 1958
			Cardio	920			
			Hemato	920			
			Hepatic	920			
			Renal	920			
13	Rat (NS)	1 d 2 hr/d	Hepatic	13070 M			Carlson 1973
14	Rat (Wistar)	10 d 24 hr/d	Hemato	800 M			Koizumi et al. 1983
			Hepatic	800 M			
15	Rat (Sprague-Dawley)	5 d 6 hr/d	Hepatic	500 M			Savolainen et al. 1977
16	Rat (Sprague-Dawley)	1 d 24hr/d	Hepatic	2500 M			Fuller et al. 1970
17	Rat (Wistar)	1 d 6-420 min/d	Bd Wt	30000			Adams et al. 1950

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
18	Rat (Sprague-Dawley)	1 d 2 hr/d	Resp	15000 M			Comish and Adefuin 1966
			Hepatic	15000 M			
			Renal	15000 M			
			Endocr	15000 M			
			Bd Wt	15000 M			
19	Rat (Wistar)	1 d 6-420 min/d	Resp	18000 M			Adams et al. 1950
			Cardio	18000 M			
			Hepatic		8000M (increased liver weight, mild fatty change)		
			Renal	18000 M			
			Bd Wt	18000 M			
20	Mouse (Swiss Webster)	1 d 10-780 min/d	Hepatic	13500 F			Gehring 1968
21	Mouse (Swiss albino)	1-6 d 4-24 hr/d	Hepatic	6000 M			Lal and Shah 1970
22	Mouse (CFW Swiss)	4 d 24 hr/d	Bd Wt	2000 M		4000 M (26% reduction in body weight)	Evans and Balster 1993
23	Dog (Beagle)	1 d 10 min/d	Cardio	2500 M		5000 M (cardiac sensitization)	Reinhardt et al. 1973
24	Dog (Beagle)	1 d 5 min/d	Cardio			7500 (EC50 for cardiac sensitization)	Clark and Tinston 1973
25	Dog (Beagle)	1 d 15min/d	Cardio	10000			Egle et al. 1976

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
26	Dog (NS)	1 d 5 min/d	Resp	25000			Herd et al. 1974
			Cardio			8000 (50 mm Hg reduction in mean blood pressure)	
			Hepatic	25000			
27	Rabbit (New Zealand)	1 d 7.5-60 min/d	Cardio			5600 M (cardiac sensitization)	Carlson 1981
	Immunological/Lymphoreticular						
28	Rat (Sprague-Dawley)	1 d 2 hr/d		15000 M			Cornish and Adefuin 1966
29	Mouse (CD-1)	1 d 3hr/d		350 F			Aranyi et al. 1986
	Neurological						
30	Human	1 d 30 min/d		250 M	350 M (increased reaction time, decreased perceptual speed and manual dexterity)		Gamberale and Hultengren 1973
31	Human	1 d 3.5 hr/d			175[b] M (decreased psychomotor performance)		Mackay et al. 1987
32	Human	5 d 6.5-7 hr/d				500 M (impaired balance)	Stewart et al. 1969
33	Human	1 d 15-186 min/d		496 M		900 M (lightheadedness)	Stewart et al. 1961
34	Human	1 d up to 2 hr/d				10000 (anesthesia)	Dornette and Jones 1960

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
35	Human	5 d 1-7.5 hr/d		350	500 (altered EEG)		Stewart et al. 1975
36	Human	1 d 5-450 min/d				920 (ataxia)	Torkelson et al. 1958
37	Monkey (Baboon)	1 d 4hr/d		1400 M	1800M (increased response time in match to sample task)		Geller et al. 1982
38	Rat (Sprague-Dawley)	1 d 6hr/d				10000 M (all somnolent)	Bonnet et al. 1980
39	Rat (Alderley Park)	1 d 10-15 min/d				5000 (EC50 for ataxia)	Clark and Tinston 1982
40	Rat (Wistar)	1 d 5-60 min/d			8000M (increased brain lactate and pyruvate)		Folbergrova et al. 1984
41	Rat (Wistar)	1 d 0.5-2 hr/d		3500 M	6000M (dizzness, decrease local cerebral glucose consumption)	7800 M (ataxia)	Hougaard et al. 1984
42	Rat (Charles River-CD)	1 d 0.5-4 hr/d		1750 M		3080 M (impaired reflexes)	Mullin and Krivanek 1982
43	Rat (Wistar)	1 d 6-420 min/ d				5000 (narcosis)	Adams et al. 1950
44	Rat (Fischer 344)	4 d 6 hr/d			1000 F (altered EEG, FEP, and SEP)		Albee et al. 1990b
45	Rat (Fischer 344)	4 d 6 hr/d				4000 (increased motor activity)	Albee et al. 1990a

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
46	Mouse (Swiss Webster)	1 d 10-780 min/d				13500 F (unconsciousness)	Gehring 1968
47	Mouse (NS)	1 d 2 hr/d				7330 (prostration)	Lazarew 1929
48	Mouse (CD-1)	1 d 20 min/d				2876 M (EC50 for effect on ability to discriminate from pentobarbital)	Rees et al. 1987a
49	Mouse (CD-1)	1 d 20 min/d				850 M (EC50 for effect on ability to discriminate from ethanol)	Rees et al. 1987b
50	Mouse (Swiss OF1)	1 d 4 hr/d				6644 M (EC50 for increased seizure threshold)	De Ceaurriz et al. 1981
51	Mouse (NS)	1 d 4 hr/d		50 M	100M (reduced cGMP in brain)		Nilsson 1986b
52	Mouse (NS)	1 d 4 hr/d		500 M	1000M (increased cAMP in brain)		Nilsson 1986a
53	Mouse (NMRI)	1 d 1hr/d		1300 M		2000 M (increased motor activity)	Kjellstrand et al. 1985a
54	Mouse (CD-1)	1 d 20 min/d				2836 M (EC50 for effect on operant behavior)	Balster et al. 1982
55	Mouse (CD-1)	1 d 30 min/d				5173 M (EC50 for impaired screen climbing ability)	Woolverton and Balster 1981
56	Mouse (Swiss OF1)	1 d 4 hr/d				2064 M (altered swimming behavior)	De Ceaurriz et al. 1983

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
57	Mouse (CD-1)	1 d 30 min/d				7129 M (EC50 for reduced fixed interval response rate)	Moser and Balster 1986
58	Mouse (CD-1)	1 d 10-60 min/d				5674 M (EC50 for impaired screen climbing ability)	Moser and Balster 1985
59	Mouse (CFW Swiss)	4 d 24 hr/d				500 M (decreased threshold to convulsions upon withdrawal)	Evans and Balster 1993
60	Dog (Beagle)	1 d 15 min/d		10000			Egle et al. 1976
	Reproductive						
61	Rat (NS)	1 d 6-420 min/d		18000 M			Adams et al. 1950
	Developmental						
62	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		875 F			Schwetz et al. 1975
63	Rat (CD)	Gd 6-15 4 hr/d		3000 F	6000 F (decreased female fetal weight, delayed ossification)		BRRC 1987a
64	Mouse (Swiss Webster)	Gd 6-15 7 hr/d		875 F			Schwetz et al. 1975
65	Rabbit (New Zealand)	Gd 6-18 6 hr/d		3000 F	6000 F (extra rib)		BRRC 1987b

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
66	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
67	Monkey (NS)	14 wk 7 d/wk 24 hr/d	Resp	1000			MacEwen and Vernot 1974
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
68	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
69	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d	Hepatic	820 M			Toftgard et al. 1981
			Bd Wt	820 M			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
70	Rat (Sprague-Dawley)	15 wk 5 d/wk 5-6 hr/d	Resp	1100 F			Truffert et al. 1977
			Hemato	1100 F			
			Hepatic	1100 F			
			Renal	1100 F			
			Bd Wt	1100 F			
71	Rat (NS)	14 wk 24 hr/d	Resp	1000			MacEwen and Vernot 1974
			Hepatic	1000			
			Renal	1000			
			Bd Wt	1000			
72	Rat (NS)	3 mo 5 d/wk 3-60 min/d	Hepatic	10000 M			Torkelson et al. 1958
			Renal	10000 M			
			Bd Wt	10000 M			
73	Rat (CDF)	90 d 5 d/wk 6 hr/d	Resp	1000	2000	(mild nasal epithelial degeneration)	Calhoun et al. 1981
			Cardio	2000			
			Gastro	2000			
			Hemato	2000			
			Musc/skel	2000			
			Hepatic	1000	2000	(reduced glycogen, fatty change)	
			Renal	2000			
			Derm	2000			
			Ocular	2000			
			Bd Wt	2000			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
74	Rat (NS)	44 d 5 d/wk 7 hr/d	Resp	5000			Adams et al. 1950
			Cardio	5000			
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			
75	Mouse (CF1)	14 wk 24 hr/d	Hepatic	250 M	1000M (fatty change, necrosis)		McNutt et al. 1975
76	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Resp	1000	2000 (mild nasal epithelial degeneration)		Calhoun et al. 1981
			Cardio	2000			
			Gastro	2000			
			Hemato	2000			
			Musc/skel	2000			
			Hepatic	1000	2000 (fatty change)		
			Renal	2000			
			Derm	2000			
			Ocular	2000			
			Bd Wt	2000			
77	Dog (Beagle)	90 d 24 hr/d	Resp	380			Prendergast et al. 1967
			Cardio	380			
			Hemato	380			
			Hepatic	380			
			Renal	380			
			Bd Wt	140		380 (body weight gain reduced 51%)	

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
78	Dog (Beagle)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt		2210 (body weight gain reduced >12%)		
79	Dog (NS)	14 wk 24 hr/d	Gastro	1000			MacEwen and Vernot 1974
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
80	Rabbit (New Zealand albino)	90 d 24 hr/d	Resp	380			Prendergast et al. 1967
			Cardio	380			
			Hemato	380			
			Hepatic	380			
			Renal	380			
			Bd Wt	140		380 (66% reduction in body weight gain)	
81	Rabbit (New Zealand albino)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt			2210 (over 34% reduction in body weight gain)	

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
82	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Resp	500			Torkelson et al. 1958
			Cardio	500			
			Hemato	500			
			Hepatic	500			
			Renal	500			
			Bd Wt	500			
83	Rabbit (NS)	44 d 5 d/wk 7 hr/d	Resp	5000 F			Adams et al. 1950
			Hepatic	5000 F			
			Renal	5000 F			
			Bd Wt		5000 F (slight decrease in body weight gain)		
84	Gerbil (Mongolian)	3 mo 24 hr/d	Bd Wt	1000			Rosengren et al. 1985
85	Gn pig (Hartley)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
86	Gn pig (NS)	3 mo 5 d/wk 3-180 min/d	Resp		1000 F (lung irritation)		Torkelson et al. 1958
			Hepatic		1000 F (fatty change)		
			Renal	2000 F			
			Bd Wt	2000 F			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
87	Gn pig (NS)	45 d 5 d/wk 7 hr/d	Resp	5000					Adams et al. 1950
			Hepatic		5000	(fatty change)			
			Renal	5000					
			Bd Wt				5000	(over 20% decrease body weight gain)	
88	Gn pig (NS)	30 d 7 hr/d	Resp	3000					Adams et al. 1950
			Cardio	3000					
			Hepatic		3000	(fatty change)			
			Renal	3000					
			Bd Wt				3000	(over 20% reduction in body weight gain)	
89	Gn pig (NS)	93 d 5 d/wk 7 hr/d	Resp	650					Adams et al. 1950
			Cardio	650					
			Hepatic	650					
			Renal	650					
			Bd Wt		650	(body weight gain reduced 18-35%)			
Immunological/Lymphoreticular									
90	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d		2210					Prendergast et al. 1967
91	Rat (Sprague-Dawley)	6 wk 5d/wk 8hr/d		2210					Prendergast et al. 1967

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
92	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		2000			Calhoun et al. 1981
93	Dog (Beagle)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
94	Rabbit (NS)	44 d 5 d/wk 7 hr/d		5000 F			Adams et al. 1950
95	Gn pig (NS)	45 d 5 d/wk 7 hr/d		5000			Adams et al. 1950
	Neurological						
96	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
97	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
98	Rat (NS)	3 mo 5 d/wk 3-60 min/d				10000 M (ataxia, narcosis)	Torkelson et al. 1958
99	Rat (Fischer 344)	13 wk 5 d/wk 6 hr/d		630	2000 (decreased forelimb grip performance)		Mattsson et al. 1993
100	Mouse (CD-1)	4 wk 4 d/wk 20 min/d			3300M (EC50 for decreased response rate)		Moser et al. 1985

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
101	Dog (Beagle)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
102	Rabbit (New Zealand albino)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
103	Gn pig (Hartley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
104	Gerbil (Mongolian)	3 mo 24 hr/d			70 (decreased DNA content in some brain areas)		Karlsson et al. 1987
105	Gerbil (Mongolian)	3 mo 24 hr/d		70 [c]		210 (increased GFA protein indicating astrogliosis)	Rosengren et al. 1985
	Reproductive						
106	Rat (NS)	44 d 5 d/wk 7 hr/d		5000 M			Adams et al. 1950
107	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		2000			Calhoun et al. 1981
108	Rabbit (NS)	6 mo 5 d/wk 7 hr/d		500 M			Torkelson et al. 1958
109	Gn pig (NS)	45 d 5 d/wk 7 hr/d			5000 M (testicular degeneration)		Adams et al. 1950

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key to figure [a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
110	Gn pig (NS)	30 d 7 hr/d		3000 M			Adams et al. 1950
	Developmental						
111	Rat Long-Evans	premating: 2 wk 5 d/wk 6 hr/d pregnancy: Gd 1-20 7 d/wk 6 hr/d			2100 F (delayed ossification, reduced clavicle)		York et al. 1982
	CHRONIC EXPOSURE						
	Systemic						
112	Human	up to 6 yr (occup)	Cardio	150			Kramer et al. 1978
			Hemato	150			
			Hepatic	150			
			Renal	150			
113	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d	Resp	1500			Quast et al. 1988
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Bd Wt		500 F (body weight reduced up to 8%)		

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
114	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d	Resp	1500			Quast et al. 1988
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Derm	1500			
			Bd Wt	1500			
Immunological/Lymphoreticular							
115	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
116	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
Neurological							
117	Human	6.7 yr avg (occup)		200 F			Maroni et al. 1977
118	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
119	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Reproductive							
120	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
121	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 2 ppm; unadjusted exposure concentration divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL)
[c]used to derive an intermediate inhalation MRL of 0.7 ppm; continuous exposure concentration divided by an uncertainty factor of 100 (10 for extrapolation from gerbils to humans and 10 for human variability)

avg = average; Bd Wt = body weight; cAMP = cyclic adenosine monophosphate; Cardio = cardiological; cGMP = cyclic guanidine monophosphate; d = day(s); Derm = dermal; DNA = deoxyribonucleic acid; EC_{50} = effective concentration, 50%; EEG = electroencephalogram; Endocr = endocrine; F = female; FEP = flash evoked potential; Gastro = gastrointestinal; Gd = gestation day; GFA = glial fibrillary acid; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NS = not specified; NOAEL = no-observed-adverse-effect level; occup = occupational; resp = respiratory; SEP = somatosensory evoked potential; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation

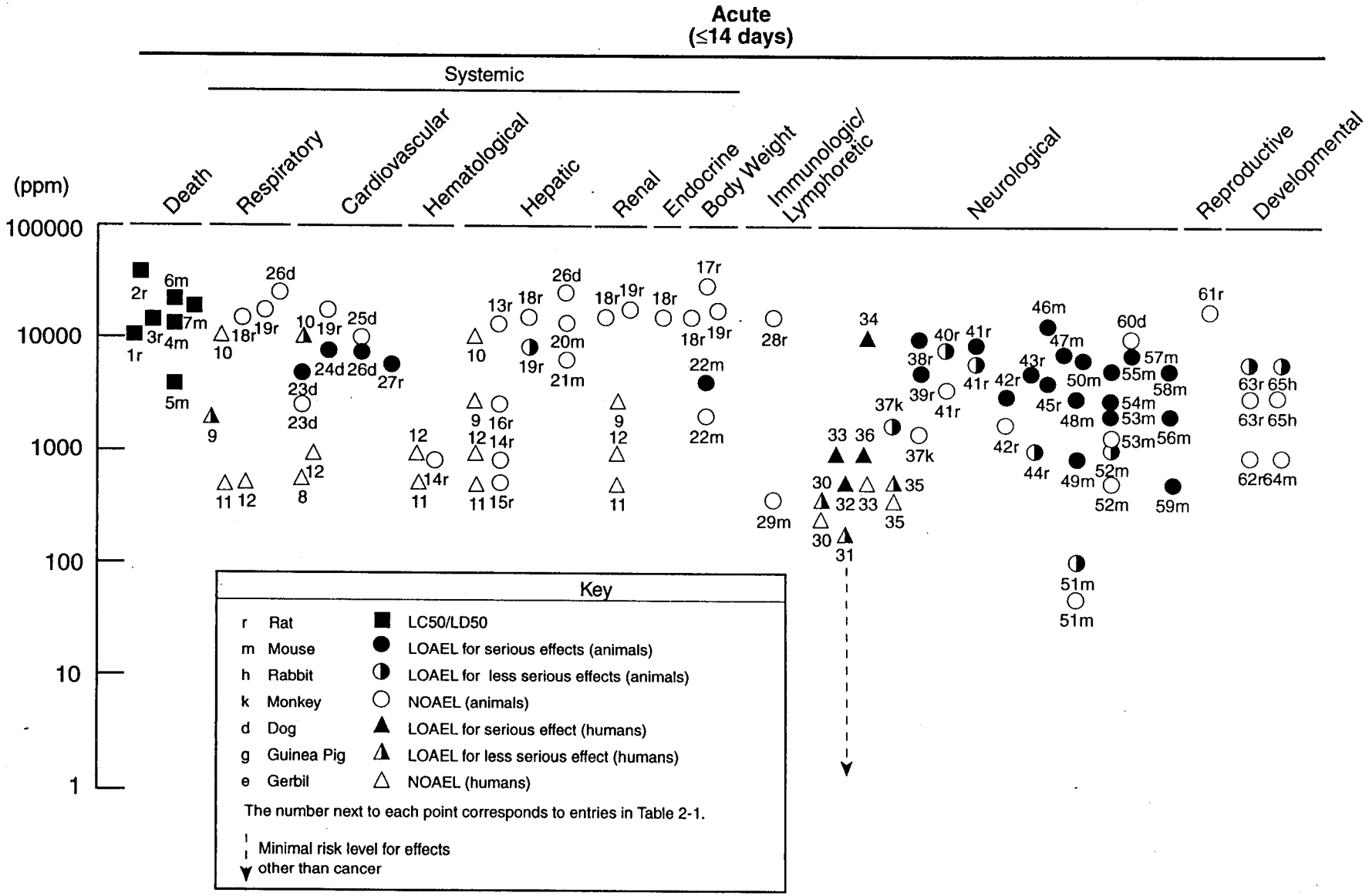


Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (continued)

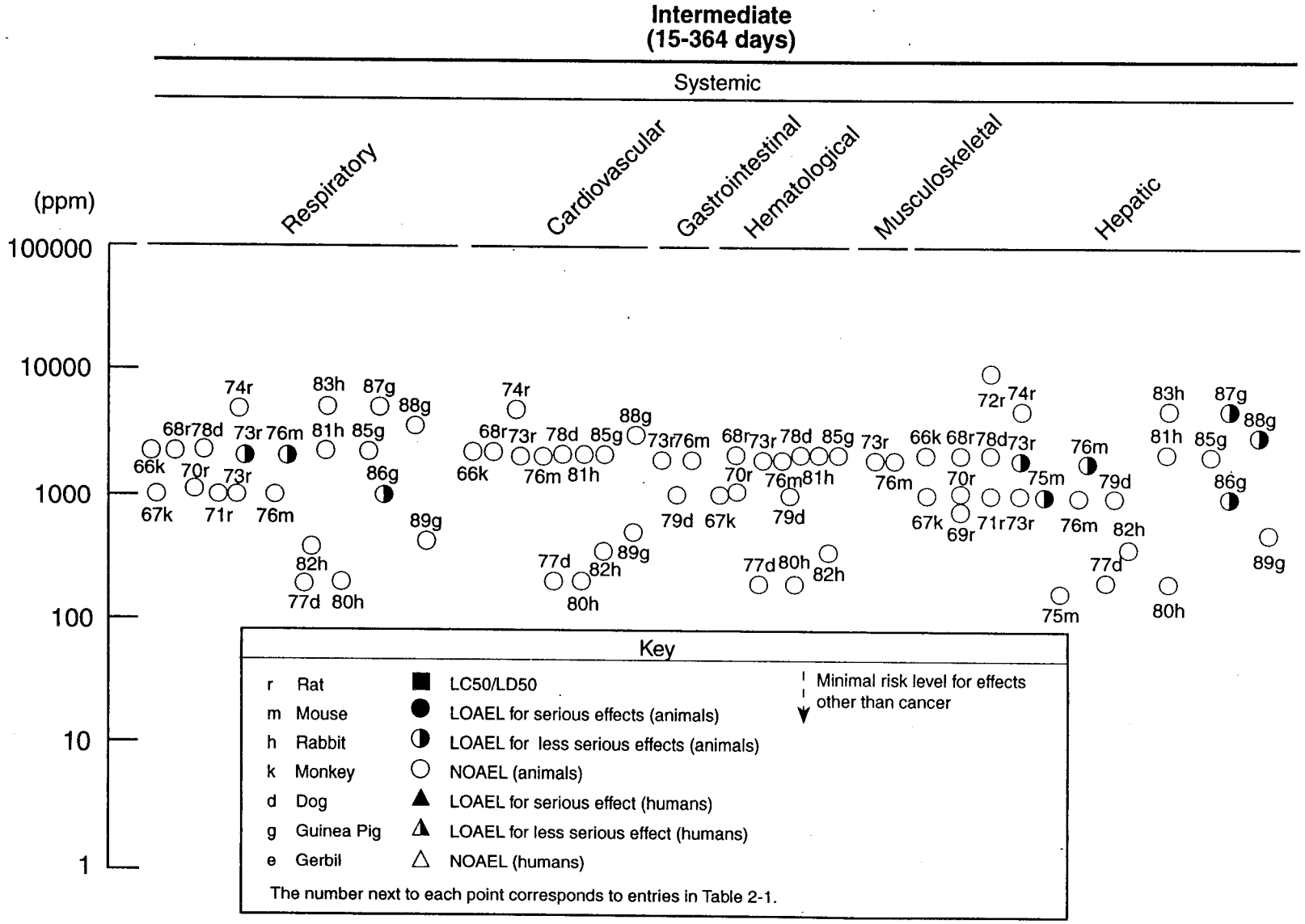


Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (continued)

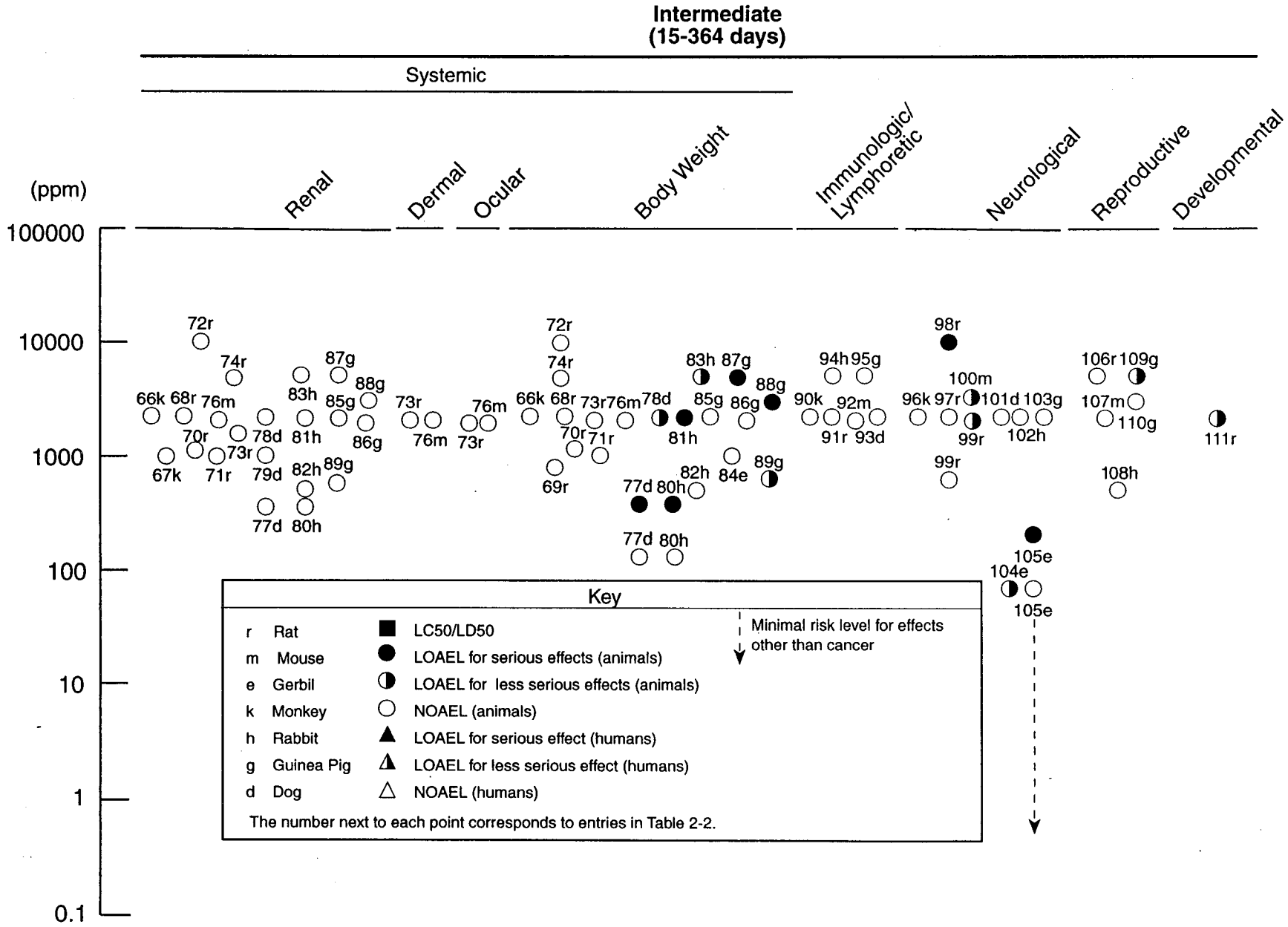
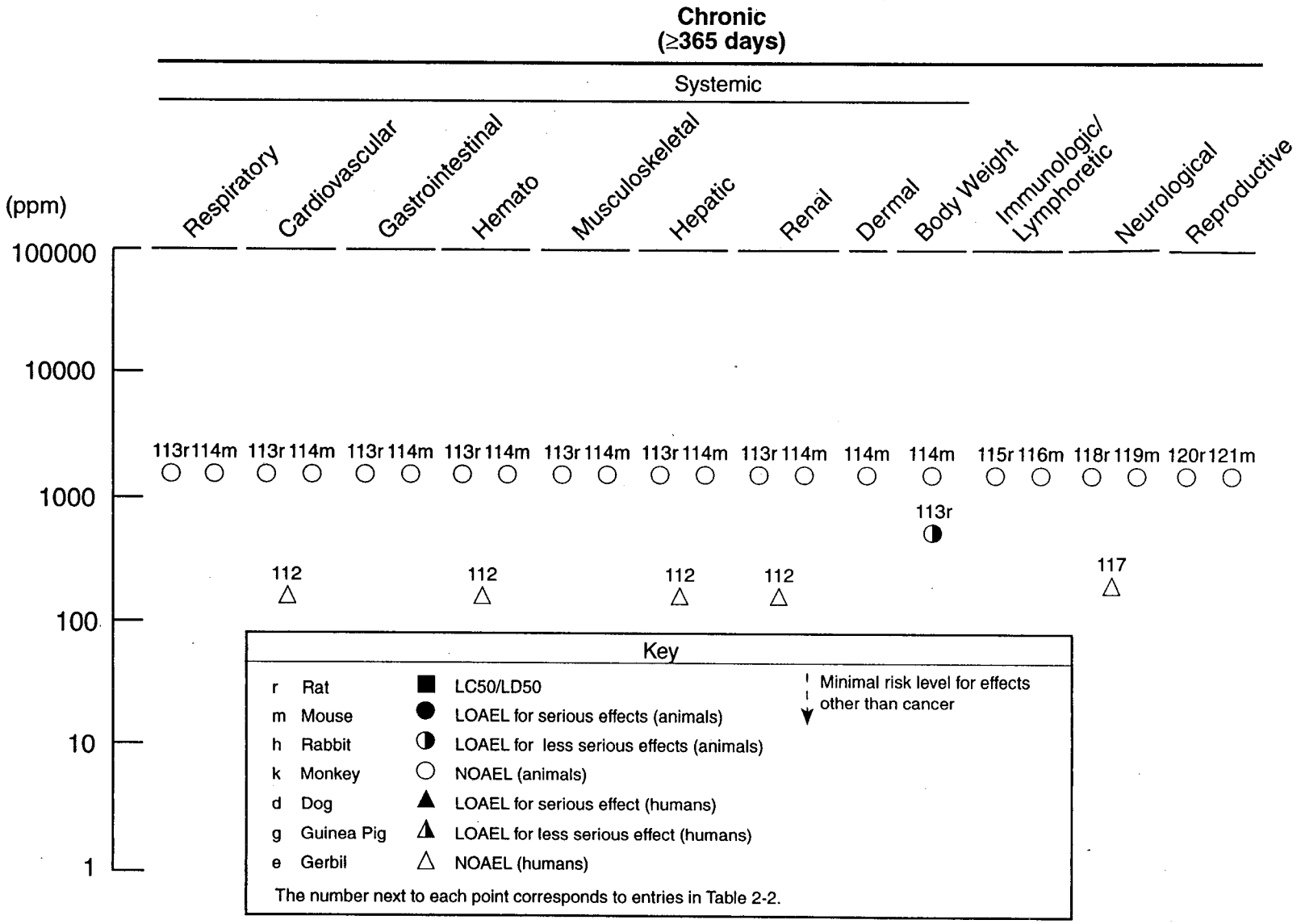


Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (continued)



and studies in animals indicate that long-term exposure to low or moderate 1,1,1-trichloroethane concentrations may not influence survival.

2.2.1.2 Systemic Effects

Respiratory Effects. In humans, acute exposure to high concentrations of 1,1,1-trichloroethane can produce respiratory depression (Kelly and Ruffing 1993), leading to death (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969). Respiratory depression may be a result of generalized central nervous system depression (see the discussion of Neurological Effects in this section). 1,1,1-Trichloroethane was not found to have produced irritation of respiratory mucous membranes. Acute exposure to lower concentrations of 1,1,1-trichloroethane in controlled studies did not affect respiratory rate or volume in humans (Domette and Jones 1960; Stewart et al. 1975; Torkelson et al. 1958). Chest radiographs from several (unspecified number) of twenty-eight workers exposed to an undetermined concentration of 1,1,1-trichloroethane for about 10 years showed changes consistent with early pneumoconiosis (fibrosis), but this was consistent with known exposure to asbestos and silica (Kelafant et al. 1994).

Death due to respiratory failure has been reported in several species of animals acutely exposed to high 1,1,1-trichloroethane concentrations (Adams et al. 1950; Krantz et al. 1959). Other data on respiratory effects in animals are limited to results of histological examinations of the lungs and related tissues. Tissue lesions were not found in rats or dogs exposed to high concentrations of 1,1,1-trichloroethane for short periods (Adams et al. 1950; Bonnet et al. 1980; Comish and Adefuin 1966; Herd et al. 1974). Exposure to moderate to high concentrations for intermediate periods (16 months) failed to produce pulmonary lesions in most species (Adams et al. 1950; Eben and Kimmerle 1974; MacEwen and Vemot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977), but irritation and inflammation occurred in the lungs of guinea pigs exposed to 1,000 ppm for 3 months (Torkelson et al. 1958). These effects were not found in other studies in which guinea pigs were exposed to lower concentrations or exposed for shorter durations (Adams et al. 1950; Prendergast et al. 1967; Torkelson et al. 1958). Rats and mice exposed to 2,000 ppm 1,1,1-trichloroethane for 3 months developed mild degeneration of the nasal olfactory epithelium (Calhoun et al. 1981). Chronic inhalation of moderate 1,1,1-trichloroethane concentrations did not produce lesions in the respiratory tissues of rats or mice (Quast et al. 1988).

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. Although lung irritation, inflammation, and olfactory epithelium degeneration were found in some species of laboratory animals exposed for intermediate durations in some studies, the weight of evidence suggests that respiratory failure in humans and animals is secondary to central nervous system depression and occurs only after acute exposure to very high concentrations.

Cardiovascular Effects. Inhalation of very high 1,1,1-trichloroethane concentrations for a short period can produce severe cardiac arrhythmias and death in humans. Arrhythmias are thought to be produced indirectly by 1,1,1-trichloroethane by sensitization of the heart to epinephrine (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Cardiac sensitization to epinephrine has also been demonstrated in animals exposed to 1,1,1-trichloroethane (Clark and Tinston 1973). In addition, reduced blood pressure, occasionally severe, has been reported in humans following brief exposure to high concentrations of 1,1,1-trichloroethane (Domette and Jones 1960; Krantz et al. 1959). Acute exposure to lower concentrations (<1,000 ppm) did not affect clinical cardiovascular parameters such as blood pressure, pulse, heart rate, or electrocardiogram in the humans tested (Gamberale and Hultengren 1973; Torkelson et al. 1958). Myocardial injury, monitored by electrocardiography and echocardiography, was reported in the case of a young male who inhaled typewriter correction fluid (Wodka and Jeong 1991). It should be noted, however, that 1,1,1-trichloroethane may have been only one of several chemicals in the correction fluid.

In humans, long-term exposure to high 1,1,1-trichloroethane vapor concentrations can have toxic effects on the heart that persist beyond the period of exposure. While experiments in animals have shown that arrhythmias produced by 1,1,1-trichloroethane and epinephrine quickly subside after the cessation of exposure (Carlson 1981; Clark and Tinston 1973), three human cases involved ventricular arrhythmias that persisted for 2 weeks or more after solvent exposure ended (McLeod et al. 1987;. Wright and Strobl 1984). In all 3 cases, the subjects had been exposed repeatedly to high (unspecified) 1,1,1-trichloroethane concentrations. Echocardiograms revealed mild left ventricular dilation in one patient and slightly dilated left atrium in another, as well as impaired left ventricle function in both (McLeod et al. 1987). Chronic exposure (<250 ppm) to 1,1,1-trichloroethane had no effect on blood pressure, heart rate, or electrocardiogram in workers surveyed in a matched-pair epidemiology study (Kramer et al. 1978). Similar results were recently reported for a group of 28

workers exposed to unspecified, but high concentrations of 1,1,1-trichloroethane for about 10 years (Kelafant et al. 1994).

Sensitization of the heart to epinephrine-induced arrhythmias has been reported in both rabbits and dogs acutely exposed to high 1,1,1-trichloroethane concentrations (5,000-7,500 ppm) (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The effect is rapid, occurring after only a few minutes of exposure, and transitory, quickly disappearing after the end of exposure. In rabbits, there was evidence that susceptibility to arrhythmia increased with exposure duration, and that 1,1,1-trichloroethane itself, not its metabolites, produced the sensitizing effect (Carlson 1981). Among dogs, the effect was similar in normal animals and those with experimentally induced myocardial infarctions; prior damage to the heart did not lower the threshold for cardiac sensitization produced by 1 ,l, 1 -trichloroethane (Trochimowicz et al. 1974).

Blood pressure was reduced in dogs acutely exposed to high concentrations of 1,1,1-trichloroethane (>7,500 ppm) (Herd et al. 1974; Krantz et al. 1959). This effect was studied in detail by Herd et al. (1974), who reported that the decrease in blood pressure began within 15 seconds of the start of exposure and grew more pronounced as exposure continued. At 8,000-15,000 ppm, the decrease in blood pressure was accompanied by increased myocardial contractility and cardiac output. A decrease in total peripheral resistance was apparently responsible for the decrease in blood pressure at these concentrations. At 20,000-25,000 ppm, blood pressure depression was caused by reductions in myocardial contractility and cardiac output. Blood pressure returned to pre-exposure values within 15 minutes after exposure, but indices of cardiac output and contractility required 45 minutes to recover. The dogs died if the blood pressure dropped too low. Histopathological changes in the heart were not found upon necropsy.

The arrhythmogenic and hypotensive properties of 1,1,1-trichloroethane have not been examined in animal studies of longer duration. Cardiovascular end points investigated in longer-term studies include heart weight and histopathology. No cardiovascular lesions were found among several animal species exposed to moderate to high concentrations (≤5,000 ppm) of 1,1,1-trichloroethane for ≤6 months (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Prendergast et al. 1967; Torkelson et al. 1958). Chronic inhalation of moderate concentrations (<2,000 ppm) of 1,1,1-trichloroethane did not produce cardiovascular lesions in rats or mice (Quast et al. 1988). The absence of effects detectable by routine histopathology in longer-term studies does not provide

convincing evidence for lack of cardiovascular effects, because even the marked acute effects were not accompanied by changes in histopathology. Overall, however, it appears that cardiotoxicity only occurs at very high exposure levels.

The highest NOAEL values and all reliable LOAEL values for cardiovascular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l. Cardiovascular effects reported in humans include sensitization of the heart to epinephrine and decreased blood pressure. Both effects were found only after brief exposure to high 1,1,1-trichloroethane concentrations. These effects were also reported in animals, in which they were studied in greater detail. Some evidence from human case reports, although not conclusive, indicates that repeated exposure to high 1,1,1-trichloroethane concentrations may result in cardiovascular effects that persist for some time after the end of exposure. This possibility has not yet been assessed in laboratory animal investigation.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea have been reported in humans exposed to high 1,1,1-trichloroethane concentrations by inhalation (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971). Other gastrointestinal end points have not been examined in humans.

Gastrointestinal effects have not been reported in animals exposed to 1,1,1-trichloroethane, although vomiting is not possible in rodents and only histological end points have been studied in animals. Gastrointestinal lesions were not observed among several species of animals exposed to moderate to high concentrations of 1,1,1-trichloroethane for intermediate or chronic durations (Adams et al. 1950; Calhoun et al. 1981; MacEwen and Vemot 1974; Quast et al. 1988; Torkelson et al. 1958). The highest NOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. Acute exposure to high 1,1,1-trichloroethane concentrations may produce nausea and related symptoms in humans, but evidence from animals suggests that longterm exposure will not produce histological changes.

Hematological Effects. No evidence exists that 1,1,1-trichloroethane produces hematological effects in humans. Hematological parameters, including white blood cell count, red blood cell count, hemoglobin, and hematocrit, were unchanged in humans acutely exposed to high or moderate concentrations of 1,1,1-trichloroethane (Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958; Wright and Strobl 1984). Hematological variables were similarly unaffected in workers chronically exposed to low-to-moderate levels of 1,1,1-trichloroethane in a matched-pair epidemiology study (Kramer et al.

1978). Hemolytic disease was suggested by increases in urinary urobilinogen in several people exposed to high levels of 1,1,1-trichloroethane (Stewart 1971; Stewart et al. 1961), but this possibility was discounted because there was no association between exposure and elevated urinary urobilinogen levels and because other indices of hematological effects were normal.

Hematological effects were not found in animals exposed to 1,1,1-trichloroethane. No exposure-related changes in hematological parameters were found following acute, intermediate, and chronic exposure to moderate to high 1,1,1-trichloroethane concentrations in several species of animals (Calhoun et al. 1981; Eben and Kimmerle 1974; Horiguchi and Horiguchi 1971; Koizumi et al. 1983; Krantz et al. 1959; MacEwen and Vemot 1974; Prendergast et al. 1967; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977).

The highest NOAEL values for hematological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-1. Existing data indicate that 1,1,1-trichloroethane does not produce hematological effects in humans or animals following inhalation exposure.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,1,1-trichloroethane.

No musculoskeletal effects were found in animals exposed to 1,1,1-trichloroethane as assessed by histopathological examination. No lesions were found in the muscles or bones of a monkey exposed to a high 1,1,1-trichloroethane concentration for 74 days (Adams et al. 1950), or in rats and mice exposed for intermediate- or chronic-durations to moderate to high concentrations of the chemical (Calhoun et al. 1981; Quast et al. 1988).

The highest NOAEL values for musculoskeletal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1. Based on existing data, 1,1,1-trichloroethane does not cause musculoskeletal effects in animals after chronic inhalation exposure. The relevance of this information to human health is unknown.

Hepatic Effects. Although there were no indications of liver effects in studies of controlled human exposure to 1,1,1-trichloroethane, data from case reports of overexposed humans suggest that this chemical may produce mild hepatic effects in humans exposed to high levels. ,

Serum levels of transaminases and other enzymes;used as indicators of hepatocellular damage (or damage to other tissues or organ systems), were not increased by acute exposure to moderate to high 1,1,1-trichloroethane concentrations in controlled human studies; liver function tests were likewise unaffected (Domette and Jones 1960; Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). However, some case studies of individuals exposed to high 1,1,1-trichloroethane concentrations did report elevated serum enzyme levels. Four individuals who had substantial occupational exposure to 1,1,1-trichloroethane had elevated serum glutamic oxaloacetic transaminase (SGOT) levels (Hodgson et al. 1989). An individual studied by Halevy et al. (1980) had elevated levels of serum bilirubin, lactate dehydrogenase (LDH), and alkaline phosphatase, as well as SGOT. It should be noted that SGOT and LDH are present in substantial amounts in myocardial cells as well as hepatocytes, and that elevations in these enzymes could have been the result of myocardial injury. Other exposed individuals did not have elevated serum enzyme levels (Stewart 1971; Wright and Strobl 1984). In some cases, histopathological examination revealed mild fatty changes in the liver of individuals exposed to high 1,1,1-trichloroethane concentrations (Caplan et al. 1976; Hall and Hine 1966; Hodgson et al. 1989). In another case, cholestasis was observed (Halevy et al. 1980). Nevertheless, hepatic changes were not observed in most cases.

Chronic exposure to low 1,1,1-trichloroethane levels (<250 ppm) did not affect serum chemistry parameters, including SGOT, serum glutamic pyruvic transaminase (SGPT), bilirubin, LDH, gamma-glutamyl transpeptidase, and alkaline phosphatase, in individuals tested as part of a matchedpair epidemiology study (Kramer et al. 1978). Results from tests for hepatic function were unremarkable in 28 workers exposed to unspecified, but high, concentrations of 1,1,1-trichloroethane for approximately 10 years (Kelafant et al. 1994).

1,1,1 -Trichloroethane produces mild hepatic effects in animals. The primary effects reported are mild histopathological changes in the liver and effects on liver enzyme activities. Acute exposure to high 1,1,1-trichloroethane concentrations did not affect serum transaminase levels in rats or mice (Carlson 1973; Comish and Adefuin 1966; Gehring 1968). An increase in transaminase levels would indicate damage to hepatocytes. The rate of deoxyribonucleic acid (DNA) synthesis in the liver also can be used as an indicator of hepatotoxicity. DNA synthesis would be expected to increase in response to cell death. Exposure to 1,100 ppm 1,1,1-trichloroethane produced a 67% increase in DNA synthesis in the. livers of exposed rats ,after 1 week; DNA synthesis returned to control levels throughout the rest of the 15-week study (Truffert et al. 1977). Corresponding histopathological changes were not found

throughout the study. Based on these data, measurement of DNA synthesis may be a more sensitive indicator of hepatocellular damage than increases in serum transaminase levels or the presence of readily observable lesions. However, these results have not been verified by additional testing. Only one study actually observed cell death following 1,1,1-trichloroethane exposure; occasional hepatocyte necrosis was seen in mice exposed to 1,000 ppm of 1,1,1-trichloroethane continuously for 14 weeks (McNutt et al. 1975). The first evidence of necrosis was not seen until after 10 weeks of exposure, but within 2 weeks of first occurrence, necrosis could be found in 40% of the exposed mice. In a study of chronic exposure, a slight decrease in the size of hepatocytes in the liver's portal region was seen in high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months (Quast et al. 1988).

The most widely reported hepatic effect in studies of 1,1,1-trichloroethane inhalation in animals is fat accumulation in the liver. Such changes are generally reversible and do not necessarily involve impairment of liver function. Histological examination following acute exposure to high concentrations revealed mild, reversible fatty changes in the livers of rats, but not dogs (Adams et al. 1950; Herd et al. 1974). Exposure duration was important in rats; effects were seen in those exposed for 7 hours, but not in those exposed to much higher concentrations for only 2 hours (Adams et al. 1950). In mice, 3-hour exposure to 800 ppm of 1,1,1-trichloroethane appeared to increase liver triglyceride levels, although controls were not included (Takahara 1986a). In studies of intermediate duration, exposure to moderate to high 1,1,1-trichloroethane concentrations produced fatty changes in the livers of rats, mice, and guinea pigs (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Fatty changes produced by 1,1,1-trichloroethane in the livers of mice continuously exposed to 1,000 ppm for 14 weeks were described in detail by McNutt et al. (1975). Prominent swelling of centrilobular hepatocytes was visible after the first week of exposure. Swelling was associated with the presence of numerous small vesicles in the cytoplasm. After 4 weeks, the number of microbodies in the cytoplasm was dramatically increased, and lysosomal vesicles were more prominent. Increased liver triglyceride levels were also reported in this study.

Studies of 1,1,1-trichloroethane's effects on liver enzyme activity are inconclusive. Acute inhalation of high concentrations induced the activity of liver microsomal enzymes (e.g., cytochrome P-450, NADPH cytochrome c reductase) in rats and mice (Fuller et al. 1970; Lal and Shah 1970). Continuous exposure to low 1,1,1-trichloroethane levels for 10 days also increased microsomal enzyme activity in rats (Koizumi et al. 1983); however, 5-day repeated exposure to a moderate concentration

decreased microsomal cytochrome P-450 enzyme activity in rats (Savolainen et al. 1977). Intermediate-duration exposure to a moderate concentration had no effect on microsomal enzyme levels in rats (Toftgaard et al. 1981).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1. Mild to moderate hepatic effects were occasionally reported in humans and animals exposed to 1,1,1-trichloroethane. These include indications of fatty liver and, in one case, cholestasis in humans and manifestations of hepatic necrosis and fatty changes in animals. These changes were not found in many studies, and results were mixed in many studies that did show effects. Evidence of hepatocellular damage and necrosis, changes in liver enzyme activity, and fat accumulation generally were reported following exposure to high concentrations in acute- and intermediate-duration studies in animals. The severity of the effects appears to be related to exposure dose and duration. It is unclear whether 1,1,1-trichloroethane may induce or inhibit microsomal enzyme activity in rats. In any case, the implications of effects on liver enzyme activity for toxicity are not clear, mainly because of the contradictory nature of the reported results.

Renal Effects. A few studies in humans have examined 1,1,1-trichloroethane's effects on select parameters of serum and urine chemistry that are related to renal function. Evidence of renal impairment was found in only one case report (Halevy et al. 1980). The individual in this case, who was exposed for 4 hours in a small room without ventilation (probably to high levels) presented with proteinuria, elevated blood creatinine, and reduced creatinine clearance, all of which were maximal at time of admission and returned to normal within 10 days. In addition to having prominent renal effects, this individual was unusual in having prominent liver effects and only minimal neurological effects. The authors suggested that an individual hypersensitivity might explain the atypical course of 1,1,1-trichloroethane intoxication. No effects were found on subsequent evaluations. No evidence of nephrotoxicity was found in other studies, although the end points examined, such as blood urea nitrogen (BUN), are only adequate for detecting serious decrements in function. An increase in the BUN level would indicate decreased elimination of nitrogenous waste by the kidneys (impairment of kidney function). Acute exposure to 1,1,1-trichloroethane had no effect on BUN or uric acid levels in humans exposed to high or moderate concentrations (Stewart 1971; Stewart et al. 1969, 1975; Wright and Strobl 1984). Chronic-duration exposure of workers to <250 ppm of 1,1,1-trichloroethane had no

effect on BUN, uric acid, or other serum indicators of nephrotoxicity in a matched-pair epidemiology study (Kramer et al. 1978).

Acute-duration exposure to high 1,1,1-trichloroethane concentrations failed to produce kidney lesions in rats (Adams et al. 1950; Bonnet et al. 1980; Comish and Adefuin 1966; Krantz et al. 1959), although relative kidney weight was increased slightly at 12,000 ppm in the one study in which it was measured (Adams et al. 1950). Exposure of several animal species to moderate to high concentrations for intermediate durations had no apparent effect on kidney weight or histopathology, or relevant serum chemistry parameters (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; MacEwen and Vemot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert .et al. 1977). Chronic inhalation of 1,1,1-trichloroethane did not affect the kidneys of rats or mice (Quast et al. 1988).

The kidney does not appear to be a target organ for 1,1,1-trichloroethane toxicity. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,1,1-trichloroethane.

Information in animals was limited to an acute-duration study in which no histopathological changes were seen in the adrenals of rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroetbane (Comish and Adefuin 1966). The NOAEL value for endocrine effects from this study is recorded in Table 2-l and plotted in Figure 2-l.

Derrmal Effects. No information was located regarding dermal effects in humans after inhalation exposure to 1,1,1-trichloroethane.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited dull fur coats (Evans and Balster 1993); this effect, however, was the result of direct contact with the chemical in the air (see Section 2.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the

incidence of dermal lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 2-1 and plotted in Figure 2-l.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). At moderate concentrations, no eye irritation was reported, even after 186 minutes.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited eye irritation during exposure (Evans and Balster 1993). All of the above effects, however, were probably due to direct contact of the chemical in the air with the eye (see Section 2.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the incidence of ocular lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 2- 1 and plotted in Figure 2- 1.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to 1,1,1-trichloroethane.

Acute inhalation exposure to high concentrations of 1,1,1-trichloroethane did not affect body weight in rats (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966). However, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days experienced a 26% reduction in body weight throughout the exposure period (Evans and Balster 1993). In studies of intermediate duration, significant reductions in body weight gain were reported in guinea pigs exposed to 650 ppm (Adams et al. 1950) and rabbits and dogs exposed continuously to 377 ppm (Prendergast et al. 1967). Other intermediate-duration studies on a variety of species (including those mentioned above) found no compound-related effects on body growth, even at high concentrations (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; Kyrklund et al. 1988; MacEwen and Vernot 1974; Prendergast et al. 1967; Rosengren et al. 1985; Toftgaard et al. 1981; Torkelson et al. 1958; Truffert et al. 1977). Body weight gain was reduced in a concentration-dependent manner in female rats chronically exposed to 1,1,1-trichloroethane (Quast et al. 1988). Body growth was not affected in male rats or male or female mice chronically exposed to the same concentrations. Food consumption was not monitored in the available studies.

Changes in body weight can be produced in a number of ways (e.g., effects on palatability of food, absorption of nutrients, energy metabolism). In the case of 1,1,1-trichloroethane, it is possible that recurring central nervous system depression produced by repeated exposure may be responsible for the reduced body weight gain, by suppression of appetite and food intake. Due to the large number of factors that might affect body weight, assessing the potential relationship between isolated occurrences of reduced body weight gain in animals and possible effects of 1,1,1-trichloroethane on growth of humans is difficult. In any case no effects from levels found near NPL hazardous waste sites would be expected.

The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects in humans after inhalation exposure to 1,1,1-trichloroethane. However, lymphoreticular effects, specifically spleen congestion, have been observed at autopsy in cases of acute accidental exposure to high concentrations of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969).

The effect of acute inhalation of 1,1,1-trichloroethane vapor on immune response in mice was studied by Aranyi et al. (1986). Mice received a single 3-hour exposure to 359 ppm of 1,1,1-trichloroethane. Susceptibility to respiratory infection was tested by challenge with *Streptococcus zooepidemicus* during exposure. Mortality was similar in test and control mice, indicating no effect on susceptibility to bacteria. To test the effect of inhalation exposure to 1,1,1-trichloroethane on the bactericidal activity of alveolar macrophages, mice were exposed to radiolabeled ^{35}S-*Klebsiella pneumoniae*, and the percentage of bacteria killed was recorded. No difference was found between test and control mice. The same results were found in both tests when mice were exposed under similar conditions for 5 days.

No histopathological alterations were observed in the spleen of rats exposed for 2 hours to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Longer-term studies of immunological effects in animals exposed to 1,1,1-trichloroethane by inhalation were limited to gross and microscopic examination of the spleen, thymus, and lymph nodes. No effect on spleen weight or, histopathology

was reported among several species exposed to moderate to high 1,1,1-trichloroethane concentrations in studies of intermediate duration (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958). No exposure-related effects were found upon histopathological examination of the spleen and thymus after chronic exposure to 11,750 ppm in rats and 1,500 ppm in mice (Quast et al. 1978, 1988).

The highest NOAEL values for immunological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l. The existing data suggest that 1,1,1-trichloroethane may not produce toxic effects on the immune system, but sensitive immunological end points have not been examined in humans or animals.

2.2.1.4 Neurological Effects

1,1,1-Trichloroethane produces central nervous system depression, increasing with exposure concentration from mild motor impairment to euphoria, unconsciousness, and death in humans. Low concentrations reportedly produce impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual ,speed, and reaction time (Gamberale and Hultengren 1973; Mackay et al. 1987). Results using subjective assessment techniques indicate that behavioral changes may not be apparent to those exposed. Syntactic reasoning remained intact, and distractibility actually improved in the study by Mackay et al. (1987), suggesting that impairment produced by 1,1,1-trichloroethane may be task-specific. In other studies, comparable exposure conditions did not produce significant psychomotor effects (Salvini et al. 1971) or produced only weak effects (Savolainen et al. 1981). Although these studies examined some of the same parameters, such as reaction time, different analytical methods were used and different subpopulations tested. Based on the LOAEL of 175 ppm for reduced performance in psychomotor tests identified by Mackay et al. (1987), an acute inhalation MRL of 2 ppm was calculated as described in the footnote in Table 2-l.

Gross neurobehavioral effects, such as disturbances of equilibrium and coordination, occur in humans following acute exposure to 1,1,1-trichloroethane concentrations between 1,000 and 2,000 ppm (Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). These effects are more obvious at higher exposure concentrations (Torkelson et al. 1958). An increase was noted in the amplitude of alpha activity in electroencephalograms from individuals acutely exposed to moderate concentrations of 1,1,1-trichloroethane (Stewart et al. 1975). The significance of this effect is unknown, especially since

it persisted for several days, but it occurred at an exposure level that produced no effect on equilibrium or coordination. Visual evoked response was not affected in this study. Complaints of lightheadedness were also reported at moderate levels (Stewart et al. 1961). High 1,1,1-trichloroethane concentrations are inhaled intentionally by some people to experience these and related effects of intoxication.

Inhalation of high 1,1,1-trichloroethane concentrations can produce anesthesia in humans (Domette and Jones 1960). Domette and Jones (1960) tested the use of 1,1,1-trichloroethane as a general anesthetic in 50 hospital patients. The effective concentration for induction of anesthesia varied from 10,000 to 26,000 ppm. Onset of anesthesia was extremely rapid, taking place within 2 minutes of the start of exposure. Maintenance of light anesthesia for ≤2 hours required 6,000-22,500 ppm. Recovery from anesthesia occurred within 5 minutes of the end of exposure. In this study, 1,1,1-trichloroethane was co-administered with nitrous oxide and oxygen, and the effect of 1,1,1-trichloroethane without nitrous oxide was not measured.

Central nervous system depression can cause respiratory failure, the most prevalent cause of death in humans exposed to high 1,1,1-trichloroethane vapor concentrations (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969). Death from inhalation of 1,1,1-trichloroethane is often preceded by unconsciousness (Gresham and Treip 1983; Travers 1974). Half of the cases of industrial overexposure to 1,1,1-trichloroethane in Great Britain between 1961 and 1980 resulted in unconsciousness; most that did not indicate unconsciousness reported other central nervous system symptoms (McCarthy and Jones 1983). In one industrial .accident (Silverstein 1983), two affected men, as well as several of their rescuers, fell unconscious.

Two studies of long-term occupational exposures found no exposure-related neurological effects. In the ,first study, the highest exposure ranged from 200 to 990 ppm (Maroni et al. 1977). No exposurerelated effects were found, based on the results of subjective questionnaires, neurological examinations, and psychological tests. The authors reported that definite conclusions as to 1,1,1-trichloroethane's neurotoxicity in humans could not be drawn due to the small study population (seven or eight subjects per group) and what the authors felt was a relatively short exposure duration (6.7-year average). In the second study, workers exposed to l-46 ppm of 1,1,1-trichloroethane were also exposed to low concentrations of toluene (1-4 ppm) and xylene (0-7 ppm) (Cherry et al. 1983). No differences were found between exposed and unexposed workers in tests of reaction time and cognition. Subjective

responses indicated greater deterioration of mood in exposed workers, but this may not have been related to exposure. The 1,1,1-trichloroethane concentrations to which workers were exposed in this study were lower than those producing effects in experimental studies. A recent study of 28 subjects occupationally exposed to high (near anesthetic levels) unspecified concentrations of 1,1,1-trichloroethane over a period of 10 years revealed deficits in memory and in several components of balance (Kelafant et al. 1994); it was the investigators's opinion that the overall evidence was suggestive of toxic exposure.

The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans. Relatively subtle behavioral effects in several species of animals have been reported following acute exposure to 1,1,1-trichloroethane concentrations in the 700-5,000 ppm range (Albee et al. 1990a; Balster et al. 1982; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a, 1990; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Woolverton and Balster 1981). These behavioral changes were readily reversible and generally involved effects on neuromuscular tests or learned behaviors. Studies using operant conditioning reflect effects of 1,1,1-trichloroethane in animals that are comparable to psychological changes in humans. Behavioral changes are generally considered to indicate neurological effects.

Neurophysiological changes have also been reported during acute inhalation exposure to 1,1,1-trichloroethane (Albee et al. 1990b). Exposure of rats to 2,000 ppm produced readily apparent changes in flash-evoked potential (FEP) and electroencephalogram (EEG), and more subtle changes in the somatosensory-evoked potential (SEP) when the rats were tested during exposure. Exposure to 1,000 ppm produced similar, but less marked, changes in the same measures. Continuous exposure of mice to moderate (500 ppm) concentrations of 1,1,1-trichloroethane for 4 days resulted in a withdrawal syndrome characterized by handling-induced seizures and reduced threshold to pentylenetetrazol-induced seizures after exposure ceased (Evans and Balster 1993). This effect could be prevented by central nervous system depressants, but not by anticonvulsants.

Acute exposure to high 1,1,1-trichloroethane concentrations produced intoxication and incoordination in rats and mice (Adams et al. 1950; Clark and Tinston 1982; Hougaard et al. 1984; Lazarew 1929), and elevation of the threshold for pentetrazole-induced seizures in mice (DeCeaurriz et al. 1981).

Exposure to 23,000 ppm produced ataxia, followed by unconsciousness and death due to respiratory failure in mice (Woolverton and Balster 1981). A progression from ataxia to lethargy, loss of motor function, and prostration produced by 1,1,1-trichloroethane has been observed in a variety of species, including rats, mice, dogs, and monkeys (Adams et al. 1950; Bonnet et al. 1980; Calhoun et al. 1988; Gehring 1968; Krantz et al. 1959; Lazarew 1929; Torkelson et al. 1958).

A recent comprehensive 13-week neurotoxicity study in rats included grip strength measures, a battery of observational measures, an electrophysiological test battery, and a neuropathology examination (Mattsson et al. 1993). The only notable finding was a significant deficit in forelimb grip performance in both male and female rats exposed to high levels (2,000 ppm) that persisted at least 7 weeks beyond the end of the exposure period. Histopathological and electrophysiological studies found no evidence of neuropathy in the forelimb that might account for this result. The authors hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible by allowing the animals to become more relaxed and, consequently, more habituated to the test procedure. No effects were found at moderate levels (630 ppm). The lack of neurophysiological effects at concentrations that produced such effects in the acute-duration study by Albee et al. (1990b) reflects the fact that testing was performed during exposure in the acute-duration study and 65 hours after the end of exposure in the intermediate-duration study.

Histopathological changes in the brain and spinal cord are not characteristic of 1,1,1-trichloroethane exposure and have not been reported when these structures have been examined (Herd et al. 1974; Krantz et al. 1959; Mattsson et al. 1993; Prendergast et al. 1967; Quast et al. 1978, 1988); however, researchers who have subjected gerbils to continuous, intermediate-duration exposure to 1,1,1-trichloroethane have reported changes in the brain that indicate physical damage. Four months after exposure had been discontinued, there was a significant increase in the level of glial fibrillary acid (GFA) protein in the sensorimotor cerebral cortex following exposure to 210 ppm of 1,1,1-trichloroethane (Rosengren et al. 1985). Since this protein is the main protein subunit of astroglial filaments and is found mainly in fibrillary astrocytes, an increase in its occurrence indicates the formation of astroglial fibrils, which are formed in response to brain injury. Therefore, increased GFA protein is associated with astrogliosis and central nervous system damage. These changes produced by 1,1,1-trichloroethane in this study were irreversible, or at least persistent. An intermediate-duration inhalation MRL of 0.7 ppm was derived for 1,1,1-trichloroethane based on the results of this study, as described in the footnote in Table 2-l. A second study, in which gerbils were exposed to 70 ppm of 1,1,1-trichloro-

ethane by the same protocol, was conducted by Karlsson et al. (1987). DNA content was used to measure cell density in different parts of the brain following exposure. Significantly decreased DNA content was found in the posterior cerebellar hemisphere, the anterior cerebellar vermis, and the hippocampus. These results could be caused by decreased cell density, possibly because of cell loss either by cell death or inhibition of nonneuronal cell acquisition in these areas, but the significance of these changes is uncertain. These methods of ascertaining physical damage to the brain have not been applied to other species.

1,1,1-Trichloroethane also produced changes in brain metabolism in rats and mice. Folbergrova et al. (1984) found a number of changes in cerebral cortical metabolism in rats exposed to high levels. Decreased glucose consumption and blood flow have also been documented in rats (Hougaard et al. 1984). Altered levels of cyclic nucleotides in the brains of mice exposed to low-to-moderate 1,1,1-trichloroethane concentrations were described by Nilsson (1986a, 1986b). The importance of the effects on cyclic nucleotides may lie in their altered capacity to act as secondary messengers within the cells, although the toxicological significance of this effect is unknown. No effect on the levels of protein, glutathione, acid proteinase, or ribonucleic acid (RNA) in the brain was found in rats acutely exposed to low concentrations of 1,1,1-trichloroethane (Savolainen et al. 1977). Continuous exposure to 1,200 ppm, but not lower doses, of 1,1,1-trichloroethane for 30 days altered the fatty acid composition of ethanolamine phosphoglyceride isolated from the cerebral cortex in rats (Kyrklund and Haglid 1991; Kyrklund et al. 1988).

1,1,1-Trichloroethane may share discriminate-stimulus properties with both pentobarbital and ethanol (Rees et al. 1987a, 1987b). Rees et al. (1987a) trained mice to press one lever in response to pentobarbital injection and another in response to saline injection. In this way, mice could “tell” the investigator when they were injected with pentobarbital. Upon inhalation of 1,1,1-trichloroethane for 20 minutes, there was a concentration-dependent increase in the percentage of time mice pressed the pentobarbital lever, indicating that the mice were generalizing the effects of pentobarbital to those of 1,1,1-trichloroethane. The results were similar in the second study (Rees et al. 1987b), in which the mice were trained to discriminate between ethanol and saline, and then exposed to 1,1,1-trichloroethane. These studies suggest that mice did not discriminate between the neurological effects of moderate to high concentrations of 1,1,1-trichloroethane and those of pentobarbital and ethanol.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1. The acute depressive effect of 1,1,1-trichloroethane in both humans and animals progresses from subtle behavioral effects .at low-to-moderate concentrations to unconsciousness at high concentrations. There is evidence to suggest that 1,1,1-trichloroethane does not produce permanent neurological effects in humans. A study in gerbils, however, has produced evidence of lasting physical damage to the nervous system (astrogliosis) following prolonged continuous exposure to low concentrations (210 ppm) of this chemical. More data are needed to determine whether these results/observations are relevant for determining human risk.

2.2.1.5 Reproductive Effects

Taskinen et al. (1989) conducted a case-control epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes.

Studies in several animal species found no evidence that 1,1,1-trichloroethane has adverse reproductive effects. Histological examination of male and female reproductive tissues following acute-, intermediate-, and chronic-duration exposure to 1,1,1-trichloroethane revealed no exposure-related changes in rats, mice, or rabbits (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977); however, varying degrees of testicular degeneration were observed in male guinea pigs exposed to 5,000 ppm 1,1,1-trichloroethane for 45 days (Adams et al. 1950). One study of intermediate duration used blood chemistry analyses to study reproductive effects. Continuous exposure to moderate levels of 1,1,1-trichloroethane vapor had no effect on butyrylcholinesterase activity in mice, which suggests that exposure did not have any effect on testosterone activity (Kjellstrand et al. 1985b). Testosterone appears to play a major role in regulating butyrylcholinesterase activity, and, although activity of this enzyme may change in the absence of an effect on testosterone, it is unlikely that an effect on testosterone levels would not be reflected by a change in butyrylcholinesterase activity.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. Based on the existing data, the reproductive system does not appear to be a target of 1,1,1-trichloroethane toxicity following inhalation exposure; however, the reproductive toxicity of this chemical cannot be evaluated fully due to the limited human data available and the lack of inhalation studies of reproductive function in animals.

2.2.1.6 Developmental Effects

Several case-control epidemiology studies investigated the relationship between adverse pregnancy outcomes (spontaneous abortions and/or congenital malformations) and maternal exposure to solvents, including 1,1,1-trichloroethane (Lindbohm et al. 1990; Taskinen et al. 1989; Windham et al. 1991). No clear evidence of a relationship between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes was found in any of these studies.

The potential developmental toxicity of inhaled 1,1,1-trichloroethane has been examined in rats and mice. Schwetz et al. (1975) exposed pregnant females of both species to moderate concentrations of 1,1,1-trichloroethane on days 6-l 5 of gestation. The only significant finding was an increase in absolute liver weight of maternal rats but not of maternal mice. Indices of embryo/fetotoxicity were comparable to controls. York et al. (1982) exposed female rats to 2,100 ppm of 1,1,1-trichloroethane for 2 weeks prior to mating and/or throughout pregnancy. There were no signs of maternal toxicity in any test group. A significant decrease in fetal body weight was observed in groups exposed either before and during pregnancy or during pregnancy only. Fetal body weights were not affected in the group exposed to 1,1,1-trichloroethane before pregnancy only. A significant increase in the incidence of delayed ossification and soft-tissue anomalies was observed only in the group that was exposed during both the premating period and gestation. Pup survival and weight gain were not affected by treatment, and neither was pup performance on neurobehavioral tests. There was no evidence of gross lesions upon necropsy at 12 months. Exposure of pregnant rats to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6-15 decreased fetal weight and delayed ossification of the cervical centrum (BRRC 1987a). Signs of maternal toxicity at this concentration included hypoactivity during exposure, perioral wetness, decreased food consumption, and increased water consumption. Maternal toxicity may have contributed to the fetotoxicity observed. Maternal toxicity and fetotoxicity were not observed in rats exposed to 3,000 ppm. Pregnant rabbits exposed to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6-18 had decreased weight gain during exposure (BRRC 1987b). A

significant increase in the incidence of extra ribs was noted in the fetuses; however, this is an anomaly often associated with maternal toxicity, regardless of the test agent. No other evidence of embryotoxicity or teratogenicity was observed in this study.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1. These data suggest that 1,1,1-trichloroethane is not a potent developmental toxin. Minor developmental effects characteristic of developmental delay were reported only at high doses and were usually accompanied by maternal toxicity.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 1,1,1-trichloroethane. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to 1,1,1-trichloroethane. A study of 1,1,1-trichloroethane vapor carcinogenicity in Fischer 344 rats and B6C3F_1 mice was conducted by Quast et al. (1988). Animals were chronically exposed to moderate to high concentrations (150-l ,500 ppm) of the chemical. In rats, no significant differences in survival were observed between groups. Body weights of treated and control rats were comparable except for a slight but significant decrease in high-dose females. Slight microscopic changes were seen in the livers of high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months. In mice, no significant differences in survival, growth, or incidence of nonneoplastic lesions were observed between groups. Pairwise comparisons between control and treated groups revealed no differences in the incidence of tumors in rats or mice. Two positive dose-related trends were statistically significant, but neither was considered treatment related. In male rats, a positive trend was evident for the incidence of benign bilateral interstitial cell tumors of the testes, a highly spontaneous tumor in the strain of rats tested. This trend disappeared when all interstitial cell tumors were combined and re-analyzed. A statistically significant trend was found for an increase in the combined incidence of benign adenomas and cystadenomas in

the lacrimal gland of female mice, but the incidences were statistically comparable to concurrent controls as well as within the historical control range. The authors point out there was no increase in the incidence of lymphoreticular proliferative processes in either species in this study. This study by Quast et al. (1988) adequately demonstrated no evidence of carcinogenicity by the inhalation route at the exposure levels used, which approach the maximum tolerated dose (MTD). An apparent increase in the occurrence of immunoblastic lymphosarcomas of the lung was reported in rats tested in an oral carcinogenicity study (Maltoni et al. 1986), described in Section 2.2.2.8.

2.2.2 Oral Exposure

2.2.2.1 Death

A single report of human oral exposure to 1,1,1-trichloroethane was found in the literature. A man survived after accidentally drinking a single ≈600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). Clinical signs of toxicity were limited to a burning sensation in the throat, nausea, and incapacitating vomiting and diarrhea.

Torkelson et al. (1958) reported acute oral LD_{50} values of 12,300 and 10,300 mg/kg for male and female rats, respectively. LD_{50} values for other species include 11,240 mg/kg for mice, 9,470 mg/kg for guinea pigs, and 5,660 mg/kg for rabbits (Torkelson et al. 1958). A more recent study reported LD_{50} values of 17,148 and 12,996 mg/kg for male and female mice, respectively (Kinkead and Wolfe 1992). In 6-week studies, lethality was produced by gavage doses of 5,620 mg/kg/day in rats and 10,000 mg/kg/day in mice (NCI 1977). Repeated gavage doses of 2,500 mg/kg/day killed 5 of 15 rats within 50 days (Bruckner 1983). In chronic studies, effects on survival occurred at much lower doses. Survival decreased in rats exposed to 750 mgfkg/day and mice exposed to 2,807 mg/kg/day by gavage (NCI 1977). Chronic oral exposure to 500 mg/kg/day of 1,1,1-trichloroethane by gavage did not affect rat survival (Maltoni et al. 1986).

Exposure to high oral doses of 1,1,1-trichloroethane can be lethal to animals and, presumably, to humans. The levels associated with decreased survival in animals appeared to decrease as exposure duration increases. Reliable LD_{50} and LOAEL values for death are recorded in Table 2-2 and plotted inFigure 2-2.

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (NS)	once (G)				12300 M (LD50)	Torkelson et al. 1958
2	Rat (NS)	once (G)				10300 F (LD50)	Torkelson et al. 1958
3	Rat (Sprague-Dawley)	once (GO)				17148 M (LD50) 12996 F (LD50)	Kinkead and Wolfe 1992
4	Mouse (NS)	once (G)				11240 (LD50)	Torkelson et al. 1958
5	Rabbit (NS)	once (G)				5660 F (LD50)	Torkelson et al. 1958
6	Gn pig (NS)	once (G)				9470 M (LD50)	Torkelson et al. 1958
	Systemic						
7	Human	once	Cardio	600M			Stewart and Andrews 1966
			Gastro		600M (vomiting, diarrhea)		
			Hemato	600M			
			Hepatic		600M (increased serum bilirubin)		
			Renal	600M			

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
8	Rat (Sprague-Dawley)	once (GO)	Hepatic	4000M			Bruckner 1983
			Renal	4000M			
			Bd Wt	4000M			
9	Rat (Sprague-Dawley)	2 wk 5 d/wk (GO)	Hepatic	10000M			Bruckner 1983
			Renal	10000M			
			Bd Wt	500M		5000 M (about 20% reduced body weight gain)	
10	Rat (NS)	7 d 1 x/d (GO)	Hepatic	1650			Platt and Cockrill 1969
			Bd Wt	1650			
11	Rat (Sprague-Dawley)	once (GO)	Hepatic		1330M (ED50 for increased SGOT)		Tyson et al. 1983
12	Rat (Wistar)	1 d (GO)	Hepatic	1370M			Vainio et al. 1976
	Neurological						
13	Human	once		600M			Stewart and Andrews 1966
14	Rat (Fischer 344)	4 d 1 x/d (GO)			705 F (altered EEG, FEP, and SEP)		Spencer et al. 1990

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Rat (Sprague-Dawley)	2 wk 5d/wk (GO)		500M		5000 M (hyperexcitability, narcosis)	Bruckner 1983
	INTERMEDIATE EXPOSURE						
	Death						
16	Rat (Sprague-Dawley)	12 wk 5 d/wk (GO)				2500 M (5/15 died)	Bruckner 1983
17	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)				5620 F (2/10 died)	NCI 1977
18	Mouse (B6C3F1)	6 wk 5 d/wk (GO)				10000 (8/10 died)	NCI 1977
	Systemic						
19	Rat (Sprague-Dawley)	12 wk 5 d/wk (GO)	Hepatic	2500M	5000M (mild, transient increased GPT, OCT)		Bruckner 1983
			Renal	5000M			
			Bd Wt	500M		2500 M (about 20% reduction in body weight gain)	
20	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	3160	5620 F (unspecified decrease in body weight gain)		NCI 1977

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
21	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	5620			NCI 1977
	Neurological						
22	Rat (Sprague-Dawley)	12 wk 5 d/wk (GO)		500M		2500 M (hyperactivity, narcosis)	Bruckner 1983
	Reproductive						
23	Rat (Sprague-Dawley)	70 d ad libitum (W)		2.96 F			NTP 1988a; George et al. 1989
24	Mouse (Swiss ICR)	25 wk ad libitum (W)		1000			Lane et al. 1982
	Developmental						
25	Rat (Sprague-Dawley)	40 d ad libitum (W)		2.4 F			NTP 1988b
26	Rat (CD)	70 d ad libitum (W)		3.50 F			NTP 1988a; George et al. 1989
27	Rat (Fischer-344	Gd 6-21 Ld 1-10 (GO)		750			Dow Chemical 1993

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
28	Mouse (Swiss ICR)	25 wk ad libitum (W)		1000			Lane et al. 1982
	CHRONIC EXPOSURE						
	Death						
29	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)				750 (survival decreased by approximately 50%)	NCI 1977
30	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				2807 F (14% decreased survival)	NCI 1977
	Systemic						
31	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Resp	1500			NCI 1977
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Derm	1500			
			Bd Wt		750 (significant raduction in body weight gain, but not quantified)		

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key[a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
32	Rat (Sprague-Dawley)	104 wk 4-5 d/wk (GO)	Bd Wt		500 F (body weight gain reduced 12% after 80 weeks)		Maltoni et al. 1986
33	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	5615			NCI 1977
			Cardio	5615			
			Gastro	5615			
			Hemato	5615			
			Musc/skel	5615			
			Hepatic	5615			
			Renal	5615			
			Derm	5615			
			Bd Wt		2807 (significant decrease in body weight gain, but not quantified)		
	Immunological/Lymphoreticular						
34	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977
35	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977
	Neurological						
36	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
37	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977
	Reproductive						
38	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977
39	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977

[a]The number corresponds to entries in Figure 2-2.

Bd Wt = body weight; Cardio = cardiological; d = day(s); Derm = dermal; ED_{50} = effective dose, 50%; EEG = electroencephalogram; F = female; FEP = flash evoked potential; (G) = gavage-not specified; Gastro = gastrointestinal; Gn pig = guinea pig; (GO) = gavage (oil); GPT = glutamic-pyruvic transaminase; Hemato = hematological; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; OCT = ornithine carbamyl transferase; NS = not specified; Resp = respiratory; SEP = somatosensory evoked potential; SGOT = serum glutamate oxaloacetate transaminase; (W) = drinking water; w = week(s); x = (times)

Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral

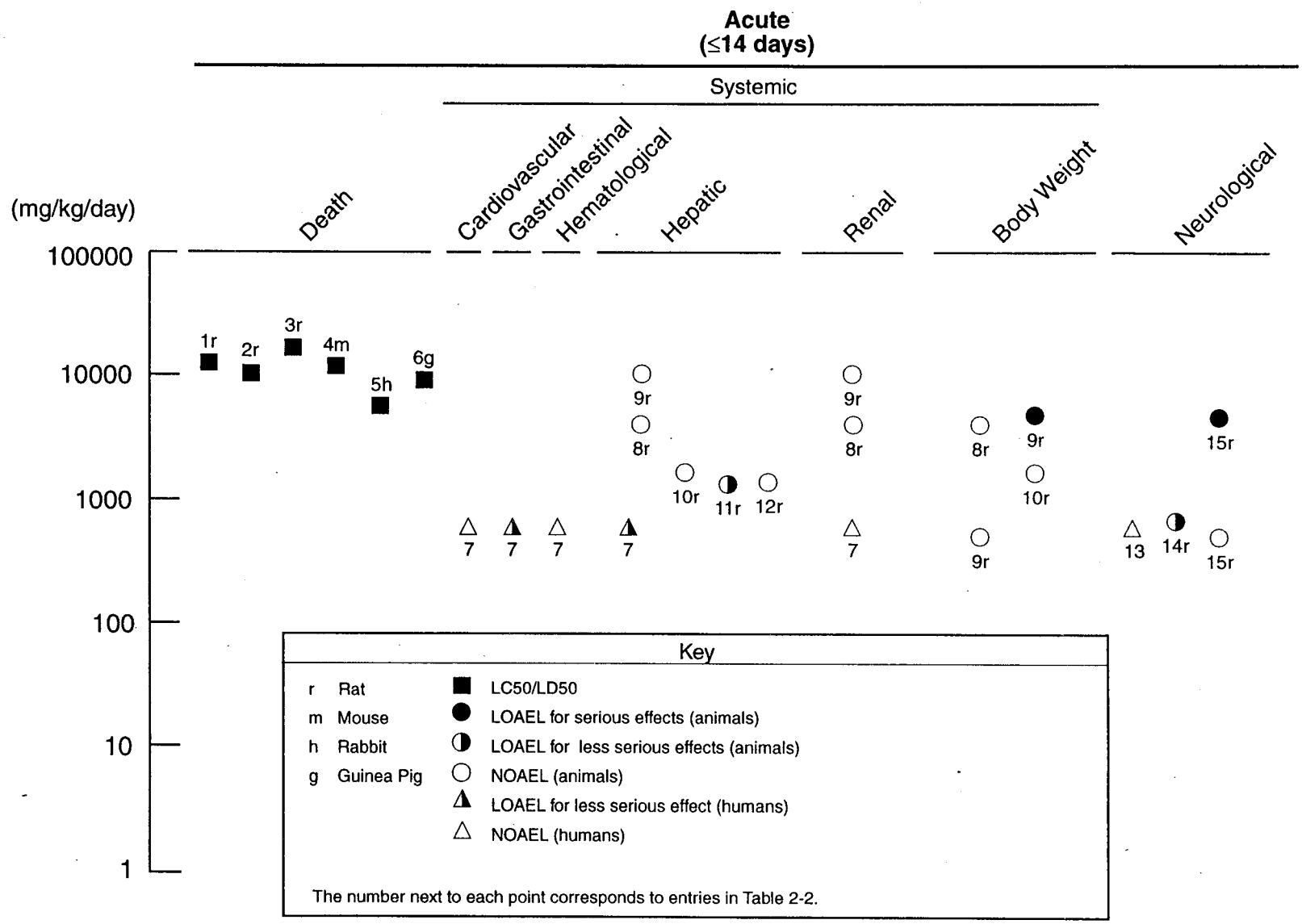


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (continued)

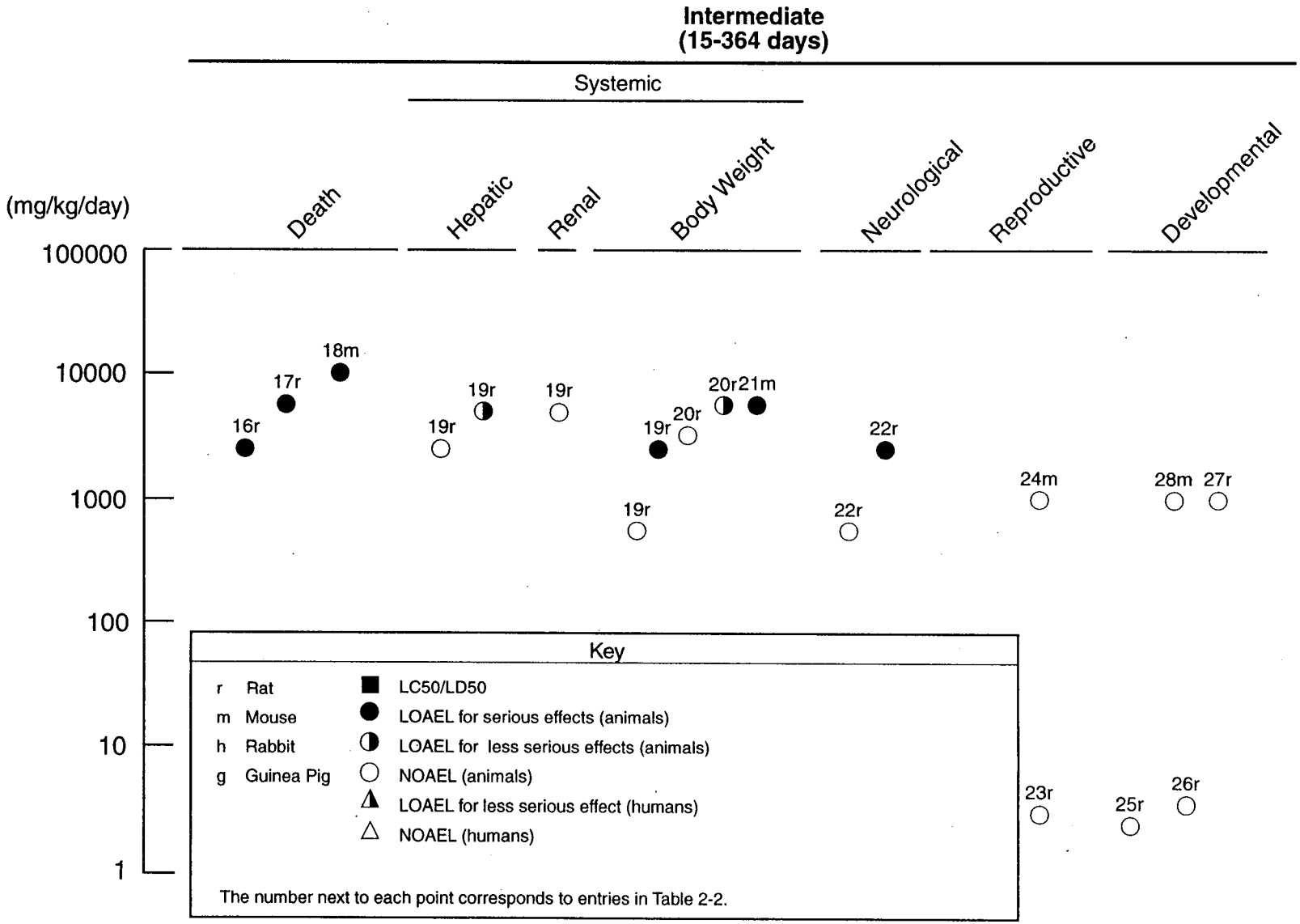
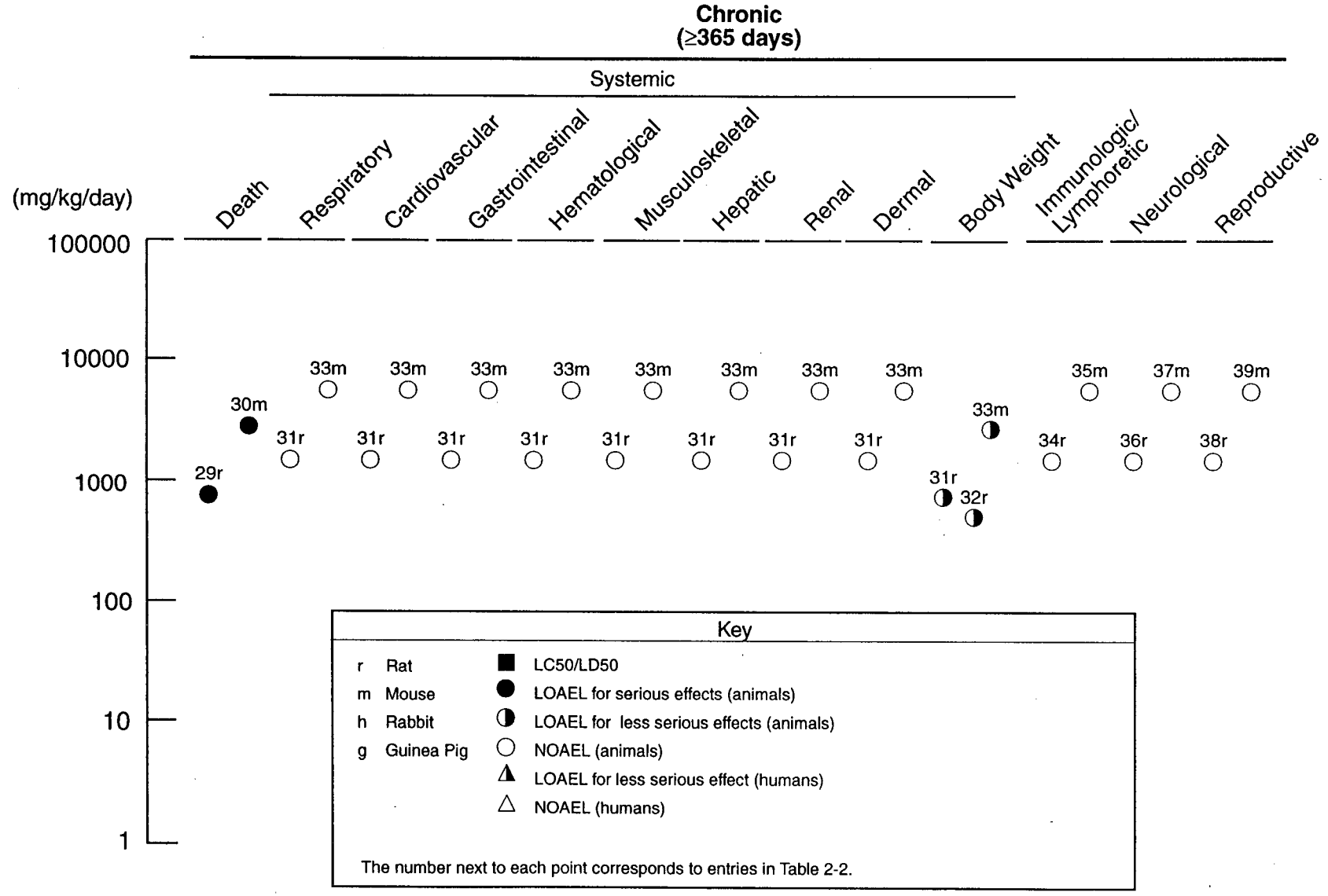


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (continued)



2.2.2.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,1,1-trichioroethane.

Only one oral study investigated the respiratory effects of 1,1,1-trichloroethane in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage did not affect the incidence of lesions in the lungs, trachea, or nasal passages (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2. Based on the negative results in the NCI (1977) study and the generally negative results in inhalation studies in which respiratory tissues came into direct contact with high levels (see Section 2.2.1.2), 1,1,1-trichloroethane is not expected to produce respiratory effects following ingestion in humans.

Cardiovascular Effects. Electrocardiogram readings were normal 4 hours after a man accidentally drank a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). Cardiovascular effects of ingested 1,1,1-trichloroethane have been investigated only by histopathological examination of exposed animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of lesions in the heart (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

The usefulness of histopathological heart examinations is limited, considering the findings of serious effects on cardiovascular function without pathological lesions in animals after acute exposure to high levels of 1,1,1-trichloroethane via inhalation. Therefore, existing data are insufficient to assess cardiovascular effects from oral exposure to 1,1,1-trichloroethane.

Gastrointestinal Effects. Severe vomiting and diarrhea began 1 hour after ingestion and continued for 6 hours in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). The patient reported feeling a burning sensation in his mouth and throat immediately after swallowing the dose.

Gastrointestinal effects of orally administered 1,1,1-trichloroethane were investigated only by histopathological examination in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice

to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the stomach, intestines, and pancreas (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

The results of the NCI (1977) study suggest that 1,1,1-trichloroethane does not produce gastrointestinal toxicity, while the case report of Stewart and Andrews (1966) shows that swallowing a large, undiluted dose of this chemical can produce severe gastrointestinal upset and some irritation of the throat.

Hematological Effects. Hematological parameters remained within normal limits in tests beginning 4 hours after exposure in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

Hematological effects were investigated only by histopathological examination in animals exposed to oral 1,1,1-trichloroethane. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the bone marrow (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

The limited data available suggest that ingested 1,1,1-trichloroethane does not produce hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated musculoskeletal effects in animals exposed to 1,1,1-trichloroethane orally. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the muscles or bones (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

Hepatic Effects. Stewart and Andrews (1966) reported a case in which a man survived drinking 1 ounce (600 mg/kg) of 1,1,1-trichloroethane. Serum transaminase levels remained within normal limits, but serum bilirubin levels became slightly elevated after 48 hours. Increased serum bilirubin

levels may result from reduced biliary excretion (i.e., cholestatic liver damage). Alternatively, hyperbilirubinemia may result from diminished hepatic conjugative metabolism of bilirubin.

Elevated SGOT levels, often seen in conjunction with hepatic damage and damage of other tissues, were reported in rats given a single oral dose of 1,330 mg/kg 1,1,1-trichloroethane (Tyson et al. 1983). Levels of SGPT, which is more specific for liver damage, remained unchanged in this study, however. Similar results in rats (little change in SGPT activity) were reported by others (Xia and Yu 1992). There were no indications of liver damage in rats given a single gavage dose of 4,000 mg/kg/day or repeated gavage doses of 10,000 mg/kg/day (Bruckner 1983). Data regarding the effect of 1,1,1-trichloroethane on the activity of rat liver enzymes are inconclusive. Increased liver microsomal and cytoplasmic protein content were found, although they were not accompanied by increases in activity of enzymes or increased liver weight (Platt and Cockrill 1969). Reduced levels of cytochrome P-450 and epoxide hydratase, suggesting inhibition of these enzymes, was reported in another study (Vainio et al. 1976). Bruckner (1983) found some evidence in rats of enzyme induction at low doses and inhibition at high doses. In an intermediate-duration study, mild liver effects (small increases in SGPT and ornithine carbamyl transferase [OCT]) occurred at 5,000 mg/kg/day (Bruckner 1983). Chronic gavage administration of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic lesions in the livers of rats or mice (NCI 1977). The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and exposure duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Human and animal studies suggest that large amounts of ingested 1,1,1-trichloroethane may produce mild hepatotoxicity ; however, whether 1,1,1-trichloroethane is an inducer or inhibitor of biotransformation enzymes following oral exposure is unclear.

Renal Effects. BUN levels were not elevated 4 hours after a man accidentally ingested a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

No effects on kidney weight or histology were found in rats given a single gavage dose of 4,000 mg/kg/day, repeated doses of 10,000 mg/kg/day, or intermediate-duration exposure to 5,000 mg/kg/day (Bruckner 1983). There was a slight transient increase in BUN in the rats repeatedly given 10,000 mg/kg/day (Bruckner 1983). Chronic gavage exposure of rats to 1,500 mg/kg/day and

mice to 5,615 mg/kg/day did not affect the incidence of nonneoplastic lesions in the kidneys (NCI 1977). NOAEL values derived from these studies are recorded in Table 2-2 and plotted in Figure 2-2. Data from animals suggest that the kidney is not a target of 1,1,1-trichloroethane taken orally. Sensitive tests of renal function have not apparently been performed, however, in animals ingesting 1,1,1-trichloroethane.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated dermal effects following oral exposure in animals. Chronic oral exposure by gavage of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic skin lesions (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2. The scarcity of data regarding dermal effects in humans or animals after oral exposure to 1 ,l ,l -trichloroethane precludes assessing potential injury of this tissue.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to 1,1,1-trichloroethane.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,1,1-trichloroethane.

Several studies monitored body weight in animals dosed orally with 1,1,1-trichloroethane. Reduced body weight gain was produced in rats by repeated doses of 5,000 mg/kg/day in an acute study and 2,500 mg/kg/day in an intermediate-duration study (Bruckner 1983). In another study, reduced body weight gain was reported at 5,620 mg/kg/day in rats exposed for 6 weeks and 750 mg/kg/day in rats exposed for 78 weeks (NCI 1977). Body weight gain in rats was reduced by an even lower dose (500 mg/kg/day) in a second chronic study, but only after 80 weeks of exposure (Maltoni et al. 1986). In mice, 5,620 mg/kg/day did not affect body weight in a 6-week study, but 2,807 mg/kg/day was sufficient to reduce body weight gain in a 78-week study (NCI 1977). These limited data on the effects of orally administered 1,1,1-trichloroethane on body weight gain in animals suggest time- and dose-response relationships.

The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,1,1-trichloroethane.

Immunological effects in animals were investigated only by histopathological examination of certain tissues. There was no effect on the incidence or type of nonneoplastic lesions in the thymus or spleen of rats or mice after chronic gavage exposure to high doses of 1,1,1-trichloroethane (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2. The scarcity of data pertaining to immunological effects in humans or animals after oral exposure to 1,1,1-trichloroethane precludes an assessment of immunotoxicity.

2.2.2.4 Neurological Effects

A thorough neurological examination (details not reported) found no abnormalities in a man who had ingested 600 mg/kg of 1,1,1-trichloroethane 4 hours earlier (Stewart and Andrews 1966).

Acute oral exposure of rats to 1,1,1-trichloroethane (705 mg/kg/day) did not result in behavior or appearance changes that could be detected after 2 days by a battery of observational measures, but did produce distinct neurophysiological alterations after 4 days. These alterations included marked changes in the flash-evoked potential (FEP) and electroencephalogram (EEG) recordings. Such effects are similar to those seen after inhalation exposure, and smaller changes in the somatosensory-evoked potential (SEP) (Spencer et al. 1990). Rats given high oral doses of 1,1,1-trichloroethane (≥2,500 mg/kg/day) exhibited a short period of hyperactivity, followed by a period of prolonged narcosis after daily dosing in acute- and intermediate-duration studies (Bruckner 1983). Neurological effects were investigated by histopathological examination of the brain and nerves in a chronic study (NCI 1977). There was no effect on the incidence or type of lesions in the brain or nerves of rats or mice after chronic gavage exposure to 1,1,1-trichloroethane (NCI 1977). Failure to detect neural lesions by routine histopathology in this study does not rule out the occurrence of neurological effects

following chronic oral exposure since physical changes in the brain did not accompany residual neurological effects seen in inhalation studies.

Reliable NOAEL and LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Limited information is available regarding the neurological effects of 1,1,1-trichloroethane following oral exposure, but the observation of narcosis in the studies by Bruckner (1983) and the results of the acute neurophysiology study in rats suggest that the neurotoxicity of orally administered 1,1,1-trichloroethane may be similar to that observed following inhalation exposure.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,1,1-trichloroethane. Reproductive effects were not found in animals orally exposed to 1,1,1-trichloroethane. A multigeneration reproduction study was conducted in mice by Lane et al. (1982). Male and female mice were exposed to 1,1,1-trichloroethane (≤1,000 mg/kg/day) in their drinking water. In the parental and F_1 generations, exposure began prior to mating and was continued through gestation and lactation. Exposure usually precedes mating by the length of the sperm cycle in studies of this type, but the duration of premating exposure for the parental generation was abbreviated in this study. Treatment did not affect maternal survival, body weight, or reproductive performance. In another study, rats were exposed to up to 3 mg 1,1,1-trichloroethane/kg/day in the drinking water from before mating through lactation (George et al. 1989; NTR 1988a). Neither maternal survival, body weight, fertility, nor the duration of gestation was affected. In a chronic-duration study in rats and mice, there was no effect on the incidence or type of nonneoplastic lesions in the prostate, seminal vesicles, testes, or epididymis in males, or the uterus or ovary in females (NCI 1977).

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. There is no evidence that oral exposure to 1,1,1-trichloroethane produces reproductive effects in animals; however, low doses were administered in one study, and the duration of premating exposure was abbreviated in the other.

2.2.2.6 Developmental Effects

The possible relationship between developmental effects and exposure to 1,1,1-trichloroethane in the drinking water was investigated in a series of epidemiology studies (Deane et al. 1989; Wrensch et al. 1990a, 1990b). A leak in an underground storage tank resulted in contamination of well water with 1,1,1-trichloroethane and other chemicals. Levels of 1,1,1-trichloroethane were far higher than levels of other chemicals (1,700 ppb when first detected, reaching a maximum of 8,800 ppb after the well was closed). An excess of miscarriages and birth defects occurred in one exposed community but not in another. Hydrogeological modeling of water and contaminant distribution within the exposed communities showed that the leak was probably not responsible for the excessive adverse pregnancy outcomes in the one community, because estimated exposure to 1,1,1-trichloroethane was lower than in the other community. Average estimated exposure, in fact, was lower in areas reporting births with malformations than in those without. A related study, conducted on a larger scale, found an excess of major cardiac anomalies during the exposure period in the service area of the water company with the contaminated well, compared to the rest of the county (Santa Clara, California) (Swan et al. 1989). Detailed analysis of the temporal and spatial distribution of cases, however, did not support the hypothesis that contamination of the well produced these adverse effects.

Lane et al. (1982) investigated the developmental effects of 1,1,1-trichloraethane in mice in a multigeneration reproduction study modified to allow screening for teratogenic and dominant lethal effects. Mice of either sex were exposed to 1,1,1-trichloroethane in their drinking water. Exposure for the initial test mice and the subsequent F_1 generation began before mating and continued throughout gestation and lactation. Exposure is usually intended to precede mating by the length of the sperm cycle; however, in this study, the duration of premating exposure for the parental generation was abbreviated. No maternal toxicity was reported. There were no treatment-related embryotoxic or fetotoxic effects in either the F_1 or F_2 generation. Pup survival and body weight were also unaffected. There was no increase in the frequency of dominant lethal factors or in the incidence of skeletal or visceral, malformations in either generation.

The developmental effects of 1,1,1-trichloroethane were also studied in rats (George et al. 1989; NTF' 1988a, 1988b). Doses of up to 3 mg/kg/day of the chemical were administered in these studies to allow comparison with preliminary results of an earlier study (Dapson et al. 1984; Hutcheon et al. 1985) that reported increased incidences of cardiovascular anomalies at these doses. In the first study

(NTP 1988a), 1,1,1-trichloroethane was added to the drinking water of male and female rats before mating and through lactation. Exposure to 1,1,1 -trichloroethane had no effect on pup survival or body weight, or on the incidence of malformed pups. Particular attention was paid to developmental effects on the cardiovascular system. There was a high incidence of patent ductus arteriosus among pups that died on postnatal day 1 (10/28 exposed versus 0/8 control). Patent ductus arteriosus was found in only one treated pup (from the low-concentration group) sacrificed on postnatal day 4. No cardiovascular anomalies of any type were found in treated pups sacrificed on postnatal day 21, which was the time that Dapson et al. (1984) reported effects. The authors explain that patent ductus arteriosus is not unexpected in pups at the earlier time points (days 1 and 4), but do not address the apparent difference between treated and control groups on day 1. Most of the pups with patent ductus arteriosus were in the low-dose group; incidence was lower in the two higher-dose groups; and the effects were not statistically significant. These results suggest that 1,1,1-trichloroethane did not affect the development of patent ductus arteriosus in these rats.

In the second study (NTP 1988b), rats were exposed to up to 2.5 mg/kg/day in the drinking water from premating through gestation. Dams were sacrificed on day 20 of gestation, and the fetuses were given comprehensive teratological examinations. No embryotoxic or fetotoxic effects were reported. There was no effect on the incidence of external, visceral, or skeletal malformations. No cardiovascular abnormalities of any type were seen.

Recently, the results of a comprehensive study in rats (Dow Chemical 1993) became available. This study examined the neurobehavioral effects of 1,1,1-trichloroethane on the offspring of rats treated with the test material by gavage on gestation day 6 through lactation day 10. The doses used were 75, 250, and 750 mg 1,1,1-trichloroethane/kg/day. The end points examined included body weight, physical maturation landmarks, motor activity, functional observation battery, brain measurements and neuropathology, and evaluation of learning capacity, task performance and short-term memory. Although sporadic difference between treated animals and controls were found with some tests, these were either not statistically significant or not dose-related, suggesting that the highest dose tested, 750 mg/kg/day, was a NOAEL for the study.

The highest NOAEL values for developmental effects in each species are recorded in Table 2-2 and plotted in Figure 2-2. The weight of evidence in experimental animal studies suggests that 1,1,1-trichloroethane is not a developmental toxicant when administered orally; however, this

conclusion is limited by the use of low doses in some of the studies. Epidemiology studies found no evidence that exposure to 1,1,1-trichloroethane was responsible for the cluster of adverse pregnancy outcomes in Santa Clara County, California.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 1,1,1-trichloroethane. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

Isacson et al. (1985) investigated the relationship between the presence of organic chemicals, including 1,1,1-trichloroethane, in drinking water and the incidence of cancer in Iowa residents. The authors contrasted towns that had detectable quantities of 1,1,1-trichloroethane in the water supply with those that did not and found no difference in the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over age 55. 1,1,1-Trichloroethane levels >0.1 μg/L (but unspecified) were detectable in this study. Assuming the average adult weighs 70 kg and drinks 2 liters of water per day, a concentration of 0.1 μg/L would produce a dose of approximately 0.000003 mg/kg/day. The authors concede that their data are not sensitive enough to support conclusions regarding the apparent lack of association between 1,1,1-trichloroethane in the water supply and cancer risk in humans. No other studies were located regarding risks of cancer in humans after oral exposure to 1,1,1-trichloroethane.

NCI (1977) conducted a bioassay for carcinogenicity of 1,1,1-trichloroethane in rats and mice. The test animals were exposed to high gavage doses of the chemical (750 or 1,500 mg/kg/day for rats and 2,807 or 5,615 mg/kg/day for mice) for 78 weeks. All animals were necropsied and the tissues examined histologically. The incidence and type of neoplasms observed were similar to those seen in untreated controls. Vehicle controls were not used in this study. There was a significant dose-related decrease in survival of both rats and mice. Among rats, no males and only 2-4% females survived to the end of the experiment. Among mice, 22-30% of treated males and 26-46% of treated females survived. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

A screening-type study using only one gavage dose level (500 mg/kg/day for 104 weeks) and a lessthan-optimal sample size (40 per sex) reported an apparent increase in leukemia incidence in rats (Maltoni et al. 1986). Survival appeared comparable between control and treatment groups, but no statistical analysis was performed. Body weight was reduced in females after 80 weeks of the experiment. Although tumor incidences were not analyzed statistically, an apparent increase in the total incidence of leukemias occurred, with 13 in treated rats and 4 in vehicle controls. The increase was due mainly to an increased incidence of immunoblastic lymphosarcomas in the lungs (seven in treated rats and one in controls). The biological and statistical significance of this finding cannot be determined because of the inherent limitations of the experimental design. The authors stated that, although definite conclusions could not be drawn based on this study, the results called for further experimentation to assess the carcinogenicity of 1,1,1-trichloroethane.

The inability to identify associations between human oral exposure and cancer incidence, as well as the limitations of the animal studies (i.e., high rate of early mortality, one dose level, small sample size), limit the assessment of potential carcinogenic effects in humans after oral exposure to 1,1,1-trichloroethane.

2.2.3 Dermal Exposure

Occupational exposure to 1,1,1-trichloroethane frequently involves both inhalation of and dermal contact with the chemical. There are many case reports of effects in individuals after occupational exposure to high levels of 1,1,1-trichloroethane, but inhalation appears to be the primary route of exposure in most such cases. Although dermal exposure may have contributed to the effects observed, these cases are discussed under Inhalation Exposure in Section 2.2.1. In a few cases, dermal exposure appeared to be more important, and these are discussed below. In all cases, except for superficial skin effects, any potential effect would likely be similar to inhalation effects at similar circulating blood levels.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,1,1-trichloroethane.

Very high dose levels were required to cause death in animals after dermal exposure to 1,1,1-trichloroethane. Exposure to 15,800 mg/kg under a cuff killed <50% of the rabbits tested (Torkelson et al. 1958). Acute dermal exposure to lower doses did not cause death in rabbits or guinea pigs (Kinkead and Leahy 1987; Torkelson et al. 1958; Wahlberg and Boman 1979). Repeated-exposure studies employing doses up to 280 mg/kg/day (covered) or 500 mg/kg/day (uncovered) did not reveal any effect on mortality in rats or rabbits (Torkelson et al. 1958; Viola et al. 1981).

These limited data suggest that dermal exposure to 1,1,1-trichloroethane is lethal only at very high doses that could not be experienced under foreseeable circumstances. The LOAEL for death in acutely exposed rabbits is recorded in Table 2-3.

2.2.3.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,1,1-trichloroethane.

Respiratory effects in animals were investigated by pathological examination of the lungs in one study. Dermal exposure for 90 days to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no effect on lung weight or the incidence of gross or microscopic lung lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 2-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to 1,1,1-trichloroethane.

Cardiovascular effects in animals were investigated by histopathological examination in one study. Intermittent 90-day dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no. effect on heart weight or the incidence of heart lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 2-3. Much higher doses may be required to produce effects by the dermal route; high vapor concentrations were required to produce cardiotoxic effects by inhalation exposure, and percutaneous absorption of 1,1,1-trichloroethane is much slower and less complete than pulmonary absorption.

TABLE 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Death						
Rabbit (NS)	1 d 24 hr/d				15800 (under 50% mortality)	Torkelson et al. 1958
Systemic						
Human	1 d 5 min/d	Derm		30 M (mild erythema)		Wahlberg 1984a
Human	10 d 1 x/d	Derm	2			Wahlberg 1984b
Rabbit (New Zealand)	1 d 24 hr/d	Bd Wt	2680 M			Kinkead and Leahy 1987
Rabbit (NS)	10 d 1x/d	Derm		35 (edema at application site)		Wahlberg 1984b
Rabbit (NS)	1 d	Ocular	50			Marzulli and Ruggles 1973
Gn pig (NS)	1 d	Bd Wt			7360 (30% reduction in body weight gain)	Wahlberg and Boman 1979
Gn pig (NS)	1 d 1/4 - 16 hr/d	Derm		1300 (epidermal degeneration)		Kronevi et al. 1981
Gn pig (NS)	10 d 1x/d	Derm		220 (edema at application site)		Wahlberg 1984b

TABLE 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE						
Systemic						
Rat (Wistar)	22 d 16 x	Gastro	280 M			Viola et al. 1981
		Hepatic		280 M (increased SGOT, OCT, GGT; hepatocellular damage)		
		Renal	280 M			
		Bd Wt			280 M (60% decrease in body weight gain)	
Rabbit (NS)	90 d 5 d/wk	Resp	500 M			Torkelson et al. 1958
		Cardio	500 M			
		Gastro	500 M			
		Hemato	500 M			
		Hepatic	500 M			
		Renal	500 M			
		Derm		15 M (mild skin irritation)		
		Bd Wt	500			
Immunological/Lymphoreticular						
Rabbit (NS)	90 d 5 d/wk		500 M			Torkelson et al. 1958
Neurological						
Rabbit (NS)	90 d 5 d/wk		500 F			Torkelson et al. 1958

TABLE 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Reproductive						
Rabbit (NS)	90 d 5 d/wk		500 M			Torkelson et al. 1958

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; Gastro = gastrointestinal; GGT = gamma-glutamyl transferase; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); OCT = orthine carbamyl transferase; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SGOT = serum glutamate oxaloacetate transaminase; wk = week(s); x = time(s)

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Gastrointestinal effects were not seen in animals dermally exposed to 1,1,1-trichloroethane. Rats exposed to 280 mg/kg/day of 1,1,1-trichloroethane under an occlusive dressing for 3 weeks showed no evidence of pancreatic damage, as determined by histopathological examination and serum lipase and amylase levels (Viola et al. 1981). Rabbits exposed to 500 mg/kg/day without occlusion for 90 days had no gross or microscopic lesions in the stomach or intestines (Torkelson et al. 1958).

These limited animal data suggest that dermal exposure to 1,1,1-trichloroethane will not result in gastrointestinal effects in humans. The NOAEL values for gastrointestinal effects in rats and rabbits are recorded in Table 2-3.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to 1,1,1-trichloroethane.

One study of hematological effects in dermally-exposed animals was located. Hematological parameters, including red blood cell count, white blood cell count, and hemoglobin, were unaffected by dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 2-3. The scarcity of human and animal data limits the assessment of hematological effects that may be caused by dermal exposure to l,l, I-trichloroethane.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to 1,1,1-trichloroethane.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,1,1-trichloroethane.

Mild hepatic effects have been reported in animals after dermal exposure to 1,1,1-trichloroethane. Levels of SGOT, omithine carbamyl transferase, and gamma-glutamyl transferase, enzymes released into the serum from damaged hepatocytes, were significantly increased in rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under occlusion in a 3-week study (Viola et al. 1981). Levels

of SGPT, another indicator of hepatic damage, were not affected. Histopathological effects, including damage to hepatocytes (fatty degeneration and mitochondrial swelling) and the presence of small focal intralobular inflammatory infiltrates, were seen in the exposed rats. A study in which rabbits were dermally exposed to higher doses of 1,1,1-trichloroethane for a longer period (but without occlusion) did not reveal histopathological effects in the liver or changes in liver weight (Torkelson et al. 1958).

Animal data suggest that dermal exposure to high doses of 1,1,1-trichloroethane may result in liver effects. Although too little information exists to allow a detailed evaluation, skin absorption is not likely to be a problem for foreseeable exposures. The NOAEL and LOAEL values for hepatic effects are recorded in Table 2-3.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Renal effects were investigated in two animal studies. Histopathological examination of the kidneys found no lesions following repeated dermal exposure to 280 mg/kg/day (covered) in rats or 500 mg/kg/day (uncovered) in rabbits (Torkelson et al. 1958; Viola et al. 1981).

The scarcity of human and animal data limits the assessment of renal effects which may be caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL values for renal effects in rats and rabbits are recorded in Table 2-3.

Dermal Effects. Dermal exposure to 1,1,1-trichloroethane causes reversible effects in humans, which increase from mild irritation to chemical burns as exposure duration increases. Volunteers who immersed their thumbs in beakers of undiluted 1,1,1-trichloroethane for 30 minutes reported mild burning pain after ≈10 minutes of exposure (Stewart and Dodd 1964). Following exposure, mild erythema and fine scaling were visible on the thumb. The scaling was easily rinsed and the erythema disappeared within 1 hour. Similar results were obtained when the entire hand was immersed in the beaker, except that the burning sensation began earlier, became more intense, and then was replaced by a feeling of cold that continued 10 minutes after exposure ended. When the subject repeatedly alternated immersion in 1,1,1-trichloroethane with exposure to air, intense cold was produced by evaporation of 1,1,1-trichloroethane from the skin. The hand remained cold for 45 minutes after the end of exposure.

Brief dermal exposure to a small amount of 1,1,1-trichloroethane covered with a glass disk produced an immediate increase in blood flow that dropped back to pre-exposure levels after 1 hour (Wahlberg 1984a). Slight, transient erythema was visible from 10 to 20 minutes following exposure. The subject reported mild stinging and burning sensations. None of these effects were found when a smaller amount of 1,1,1-trichloroethane was allowed to spread freely on the subject's skin, probably due to rapid evaporation of the chemical (Wahlberg 1984a). Repeated uncovered application of a small amount had no effect on skin-fold thickness and produced no visible dermal reaction (Wahlberg 1984b).

One case of allergic contact dermatitis from 1,1,1-trichloroethane was located in the literature (Ingber 1991). A worker whose job included using 1,1,1-trichloroethane to clean metal plates developed severe acute hand eczema soon after starting the job. The eczema persisted throughout 3 years of employment. Patch tests at that time showed a positive reaction to 1,1,1-trichloroethane. The eczema disappeared after a few weeks when contact with 1,1,1-trichloroethane was avoided. The possibility the allergic reaction to being caused by 1,1,1-trichloroethane stabilizer was not discussed.

Assessments of the skin irritancy of 1,1,1-trichloroethane in animals reveal slight to moderate reactions. Based on single-application studies in rabbits, 1,1,1-trichloroethane was ranked as a moderate skin irritant by Duprat et al. (1976). Torkelson et al. (1958), however, reported only slight reddening and scaliness of rabbits' skin following a single application. Irritation observed following repeated application of the compound for 10 days was only slightly more noticeable and quickly disappeared after the end of treatment (Torkelson et al. 1958). Skin-fold thickness increased 41-81% in rabbits and guinea pigs exposed repeatedly to dermal applications of 1,1,1-trichloroethane, and visible erythema and edema were present within 24 to 72 hours of the original exposure (Wahlberg 1984b). Intermediate-duration exposure to doses ranging from 15 to 500 mg/kg/day produced only slight, reversible irritation at the application site (Torkelson et al. 1958). Lack of dose and exposure methodology information makes it difficult to compare the results of these studies, but the weight of evidence suggests that 1,1,1-trichloroethane is not a strong dermal irritant in animals.

Kronevi et al. (1981) studied cellular changes produced in the intact skin of guinea pigs by exposure to 1 mL of undiluted 1,1,1-trichloroethane under a cover glass for durations ranging from 15 minutes to 16 hours. No gross effects were observed, indicating that the overall irritation produced was minor, but a host of degenerative changes in the epidermis, including karyopyknosis, karyolysis, perinuclear

edema, and spongiosis, was found by histological examination. Focal junctional separation and cellular infiltration were observed in the upper part of the dermis. Effects were seen within 15 minutes of exposure, and some were still evident 16 hours later.

Exposure to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours caused the fur coat of mice to become dull (Evans and Balster 1993). This effect was most likely caused by direct contact of the chemical with the skin (see also Section 2.2.1.2).

Although extended dermal contact with relatively concentrated 1,1,1-trichloroethane may cause irritation and burning sensations of the skin of humans, most evidence in humans and animals indicates that this compound is not a strong skin irritant. There is one report of a 1,1,1-trichloroethane formulation acting as a skin sensitizer in humans. The highest NOAEL values and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 2-3.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). This effect was most likely due to direct contact of the chemical with the eye.

Ocular administration of 1,1,1-trichloroethane caused only mild eye irritation in rabbits (Duprat et al. 1976; Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958). The study by Marzulli and Ruggles (1973) was a survey in which 10 laboratories conducted the Draize eye test in rabbits using 1,1,1-trichloroethane and reported little or no eye irritation.

Although eye irritation produced by direct application of 1,1,1-trichloroethane seems to be minor, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours exhibited eye irritation during exposure (Evans and Balster 1993). The highest NOAEL values and all reliable LOAEL values for ocular effects in each species and duration category are recorded in Table 2-3.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to 1,1,1-trichloroethane.

Animal studies have investigated the effect of topical 1,1,1-trichloroethane application on body weight. Acute exposure to 7,360 mg/kg of 1,1,1-trichloroethane (covered) decreased body weight gain in

guinea pigs (Wahlberg and Boman 1979). A lower dose had no effect on body weight in rabbits (Kinkead and Leahy 1987). Intermediate exposure to 280 mg/kg/day under occlusion reduced growth in rats (Viola et al. 1981). Exposure to a higher dose for a longer period did not affect rabbit body growth, but 1,1,1-trichloroethane was applied uncovered in this study (Torkelson et al. 1958). Food consumption was not monitored in these studies. Effects of 1,1,1-trichloroethane on body weight may have been produced by effects on appetite and food intake secondary to central nervous system depression, rather than physiological effects on growth and development.

The scarcity of human and animal data limits the assessment of body weight effects caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL and LOAEL values for body weight changes are recorded in Table 2-3.

2.2.3.3 Immunological and Lymphoreticular Effects

One report of a worker who developed allergic contact dermatitis to a formulation of 1,1,1-trichloroethane (Ingber 1991) is discussed in more detail under Dermal Effects in Section 2.2.3.2.

In animals, immunological effects following dermal exposure were investigated only by histopathological examination. No lesions or weight changes were found in the spleens of rabbits exposed to moderate 1,1,1-trichloroethane levels (500 mg/kg/day; no occlusion) in a 90-day study (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 2-3. The scarcity of human and animal data precludes the assessment of potential effects on immune system tissues and function after dermal exposure to 1,1,1-trichloroethane.

2.2.3.4 Neurological Effects

Three women developed peripheral neuropathy after frequent, prolonged dermal contact with formulations of 1,1,1-trichloroethane and other chemicals at their workplace (Howse et al. 1989; Liss 1988). The women initially complained of numbness in their limbs, and subsequent nerve conduction studies showed alterations in peripheral nerve activity. The effect was diagnosed as primarily a distal sensory peripheral neuropathy. These cases were unusual because the effect was greater in the hands than in the feet, the reverse of most peripheral neuropathies. Sural nerve biopsies in two of the women performed 3-4 years after diagnosis revealed chronic neuropathy (axonopathy and

myelinopathy) (Liss 1988). The authors did not establish a causal relationship with 1,1,1-trichloroethane.

Dermal studies including tests of neurological function in animals were not located. Neurological effects were investigated by histopathological examination of the brain in one study. The value of these data is limited, however, since physical changes in the brain have not been found to accompany serious neurological effects in high level inhalation studies. No lesions or weight changes were found in the brains of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 2-3. These data are not sufficient for assessing the neurotoxicity of 1,1,1-trichloroethane after dermal exposure to the compound.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to 1,1,1-trichloroethane.

Reproductive effects following dermal exposure were investigated only by histopathological examination in animals. No lesions or weight changes were found in the testes of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 2-3. The absence of human data, tests in female laboratory animals, and evaluation of reproductive function prevents an acceptable assessment of possible reproductive effects from dermally administered 1,1,1-trichloroethane.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to 1,1,1-trichloroethane.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 1,1,1-trichloroethane. Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 1,1,1 -trichloroethane.

2.3 TOXICOKINETICS

Upon first exposure, 1,1,1-trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure.

1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine; other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. (The acetylene is formed by reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply.) Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure. The toxicokinetic behavior of 1,1,1-trichloroethane has the same qualitative pattern in humans, rats, and mice; however, some quantitative differences among these species have been observed, including a higher blood:air partition coefficient and an increased rate of metabolism in mice compared with rats and humans. Physiologically-based pharmacokinetic models have been developed to describe the

kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Leung 1992; Nolan et al. 1984; Reitz et al. 1988; USAF 1990).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Data from experiments in which humans were exposed for short periods to 1,1,1-trichloroethane vapors indicate that the compound is rapidly and extensively absorbed by the respiratory system. 1,1,1-Trichloroethane was detected in the arterial blood of men within ≈10 seconds after exposure to 250 or 350 ppm (Astrand et al. 1973). When subjects held single breaths of air containing radiolabeled 1,1,1-trichioroethane for 15-40 seconds, alveolar concentrations decreased to between 10 and 20% of the initial concentrations, indicating extensive absorption upon initial exposure (Morgan et al. 1972a, 1972b). The extent of absorption of inhaled 1,1,1-trichloroethane decreases with continued exposure to the compound, as concentrations in alveolar air, blood, and tissues attain near equilibrium or steady state. Average lung retentions of 25-30% were measured in humans exposed to 35-350 ppm for 4-6 hours (i.e., the concentration of 1,1,1-trichloroethane in expired air after 4-6 hours of exposure equaled 70-75% of the inspired concentration) (Monster et al. 1979; Nolan et al. 1984). Physical exercise during 0.5-4-hour exposures increased systemic absorption of 1,1,1-trichloroethane, due to increased alveolar ventilation and cardiac output (Astrand et al. 1973; Monster et al. 1979). While steady-state levels in blood are approached within the first hours after exposure begins (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984), Nolan et al. (1984) predicted, using a physiologically-based kinetic model, that 12 consecutive and continuous daily exposures (presumably to concentrations of 350 ppm) would be required for l,I,l-trichloroethane in body tissues to reach 95% of steady state. Absorption is expected to be relatively low after steady state is reached, because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading (which in turn are affected by respective blood:air and tissue:blood partition coefficients), tissue volumes and blood flows, and low metabolism. Bloodair partition coefficients for humans, rats, and mice were 2.53, 5.76, and 10.8, respectively (Reitz et al. 1988), meaning that small rodents will experience greater systemic uptake than humans, with mice receiving the highest dose. Mice also have the highest respiratory and circulatory rates, two additional factors that significantly

influence systemic absorption of I, 1,l -trichloroethane. 1,1,1-Trichloroethane is poorly metabolized (Dallas et al. 1989) (see Section 2.3.3.).

Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate. In rats exposed to 50 or 500 ppm, percentage uptake decreased from ≈80% at the onset of exposure to ≈50% after 2 hours of exposure to 50 or 500 ppm. 1,1,1-Trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure and approached steady-state concentrations within 2 hours (Dallas et al. 1989). In anesthetized dogs under regulated respiration conditions, 1,1,1-trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure to 700, 1,500, or 3,000 ppm. Arterial blood concentrations approached steady-state levels within 1 hour at 700 ppm, but not at 1,500 or 3,000 ppm; absorption increased with increases in pulmonary ventilation rate (Hobara et al. 1982, 1983).

2.3.1.2 Oral Exposure

Data regarding the rate or extent of absorption of in,gested 1,1,1-trichloroethane in humans are not available, but based on extensive animal data, it is anticipated that oral absorption of 1,1,1-trichloroethane will be extensive in humans. Animal experiments indicate that 1,1,1-trichloroethane is rapidly and completely absorbed by the gastrointestinal tract. Maximum levels of 1,1,1-trichloroethane in venous blood of rats were detected within 10-15 minutes of gavage administration of a 14.2 mg/kg dose in water (Reitz et al. 1988). In experiments in which rats were given an 8-hour free access to drinking water containing [2-^{14}C]-labeled 1,1,1-trichloroethane, radioactivity in expired air, urine, and selected tissues (assayed 56 hours following cessation of access to the labeled water) represented 95.2% of the average dose of 116 mg/kg, indicating nearly complete absorption of the administered dose (Reitz et al. 1988). In experiments with rats and mice given single gavage doses of radiolabeled 1,1,1-trichloroethane in vegetable oil ranging from 100 to 3,000 mg/kg, dose-recovery in expired air ranged from 90 to 97% (RTI 1987). Nearly complete absorption of orally administered 1,1,1-trichloroethane was also indicated in experiments in which rats or mice were pretreated with daily doses of the compound in corn oil for 4 weeks (3,000 and 1,000 mg/kg/day for rats and mice, respectively) before radiolabeled compound was administered to measure absorption and elimination. Radioactivity in expired air and urine (collected for 48 hours after administration) accounted for 88-98% of the administered doses (Mitoma et al. 1985).

Absorption from the gastrointestinal tract is more rapid for 1,1,1-trichloroethane given in water than in vegetable oils, because the oils act as a reservoir for the chemical in the gut, so that most of the chemical remains in the oil in the gut until the oil is digested and absorbed.

2.3.1.3 Dermal Exposure

1,1,1-Trichloroethane is absorbed through human skin. The compound was detected in alveolar air of volunteers during 30minute skin absorption experiments (Stewart and Dodd 1964). The skin was exposed to the undiluted compound by thumb or hand immersion or topical application to the hand. The amount of 1,1,1-trichloroethane absorbed depended on the surface area of exposed skin and the method of exposure (i.e., immersion or topical application). 1,1,1-Trichloroethane concentrations in blood and alveolar air were 3-4 μg/mL and 2-5 ppm, respectively, immediately following the last of three daily, 2-hour exposures of 12.5 cm^2 areas of covered forearm skin in experiments with other subjects (Fukabori et al. 1977). Dermal absorption rates were 45.7 nmo/minute/cm^2 in mice after 2.92-cm^2 areas of skin were exposed to undiluted compound for 15 minutes under occluded conditions to prevent evaporative loss (Tsuruta 1975). In rats, ≈30% of a 2 mL volume of undiluted 1,1,1-trichloroethane was absorbed by a 3.1-cm^2 area of skin in 24 hours under occluded conditions (Morgan et al. 1991). It should be noted that under occluded conditions, which prevent evaporation, concentrated 1,1,1-trichloroethane will defat the skin and promote its own systemic absorption by disrupting the stratum comeum, the actual barrier to penetration. These are not conditions likely to occur in exposed people, however. There is no information available on the extent and rapidity of percutaneous absorption of 1,1,1-trichloroethane from aqueous solutions, a far more likely source of dermal contact, albeit at much lower dose rates.

1,1,1-Trichloroethane vapors will be absorbed through exposed skin to some extent, although absorption through the respiratory tract will predominate during whole-body exposure. Quantitative examination of the relative magnitudes of percutaneous and respiratory absorption in humans equipped with respiratory protection showed that a whole-body exposure to 600 ppm 1,1,1-trichloroethane for 3.5 hours would deliver a dermal dose equivalent to an absorbed inhalation dose from exposure to only ≈0.6 ppm over the same period (Riihimaki and Pfaffli 1978).

2.3.2 Distribution

2.3.2.1 inhalation Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissues after inhalation exposure. Nevertheless, 30 autopsies revealed detectable levels of the compound in subcutaneous and renal fat, liver, lung, and muscle (Alles et al. 1988).

Animal studies indicate that inhaled 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, with preferential distribution to fatty tissues. 1,1,1-Trichloroethane is rapidly cleared from tissues after exposure ceases (Holmberg et al. 1977; Schumann et al. 1982a; Takahara 1986b). Concentrations of 1,1,1-trichloroethane were higher in the liver than in the blood, kidneys, and brain of mice exposed to 10-10,000 ppm for 0.5-24 hours (fatty tissues were not analyzed separately in'this study) (Holmberg et al. 1977). In mice exposed to 1,000 ppm for 1 hour, tissue concentrations immediately after exposure displayed the following order: fat > liver > kidney > spleen = blood > lung = heart = brain (Takahara 1986b). In mice and rats exposed to 150 or 1,500 ppm 1,1,1-trichloroethane for 6 hours, concentrations were much (≈11-26-fold) higher in fatty tissue than concentrations in the liver and kidneys immediately following exposure (Schumann et al. 1982a). Experiments in which pregnant mice were exposed by inhalation to 1 ,l, 1-trichloroethane showed that the compound also is distributed to fetuses (Shimada 1988; Danielsson et al. 1986). Following a l-hour exposure of pregnant mice to 1,000 ppm, concentrations of 1,1,1-trichloroethane in maternal organs, fetuses, and placentas ranked in the following order: fat > blood > kidney > liver > placenta > brain > fetus (Shimada 1988).

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissue after oral exposure to the compound. Ingested 1,1,1-trichloroethane, however, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results of animal studies. Distribution of 1,1,1-trichloroethane to tissues will be governed by several factors, including tissue blood flow rate, tissue volume and tissue: blood partition coefficient, the latter factor being probably the most important. Following gavage administration of 1,1,1-trichloroethane in vegetable oil to rats

(100, 300, or 1,000 mg/kg) or mice (300, 1,000, or 3,000 mg/kg), the compound was distributed to tissues throughout the body, with preferential accumulation in fatty tissues (RTI 1987).

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane among human or animal tissues following dermal exposure; however, dermally applied 1,1,1-trichloroethane, once absorbed, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results from oral and inhalation studies with animals.

2.3.2.4 Other Routes of Exposure

Measurements of the tissue distribution of ^{14}C-1,1,1-trichloroethane or its metabolites in rats or mice 24 hours after an intravenous injection indicate a distribution pattern similar to that after oral or inhalation exposure; adipose tissue contained higher concentrations than skeletal muscle, liver, or skin tissue (RTI 1987).

2.3.3 Metabolism

Metabolism appears to play a relatively minor role in the overall disposition of 1,1,1-trichloroethane in humans and animals. Only a small fraction of the absorbed dose (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of the exposure route. In humans exposed to 70 or 145 ppm 1,1,1-trichloroethane in air for 4 hours, an estimated 60-30% of the absorbed compound was excreted unchanged in exhaled breath (Monster et al. 1979). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5% of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5-6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984).

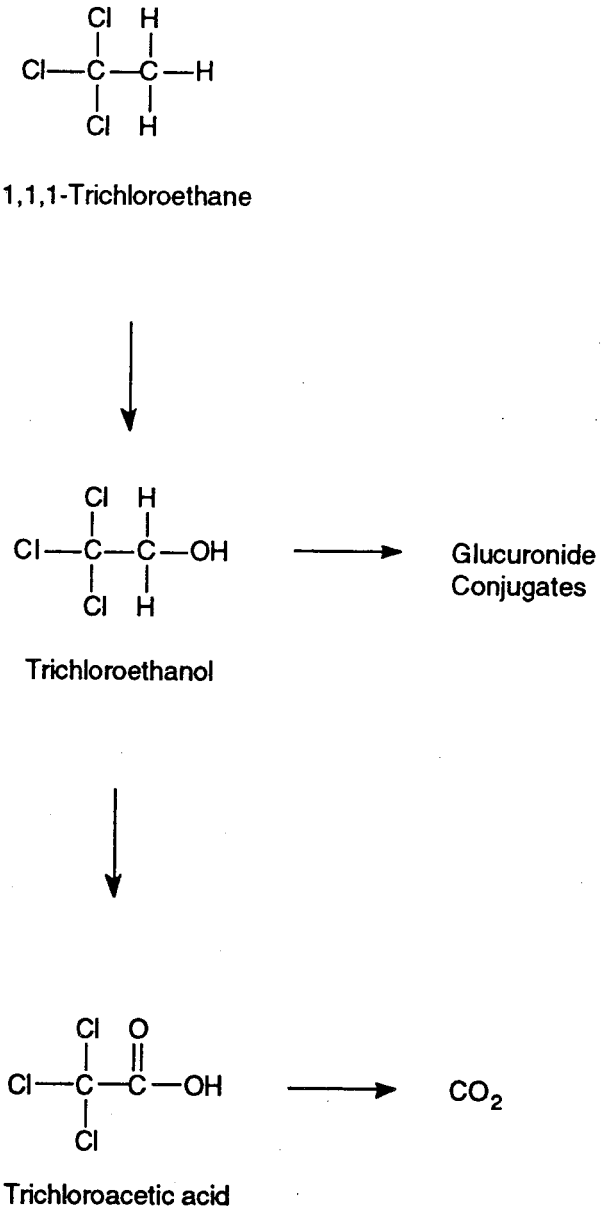
In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of ^{14}C-labeled compound, 85.1 and 92.3% of the respective doses were recovered as unchanged compound in expired air; respective recovery percentages of metabolite

fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). Similarly, exhalation of unchanged compound was the predominant pathway for elimination of absorbed 1,1,1-trichloroethane, accounting for >90% of doses administered in drinking water studies with rats (Reitz et al. 1988) and in inhalation studies with rats and mice (Schumann et al. 1982a). Comparison of metabolic disposition in mice and rats indicated that mice metabolized 2-3 times more 1,1,1-trichloroethane on a body weight basis; however, in both species, metabolism was a dosedependent, saturable process that represented a minor route of elimination (Schumann et al. 1982a, 1982b).

Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2 identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 2-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. *In vitro* reaction mixtures containing rat hepatic microsomes and nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidize 1,1,1-trichloroethane to trichloroethanol. 1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981;. Koizumi et al. 1983). The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate. formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as *in vitro* metabolic products of. 1,1,1-trichloroethane with rat hepatic microsomal cytochrome P-450 preparations (Ivanetich and Van den Honert 1981; Koizumi et al. 1983), *in vitro* production of chloral hydrate from 1,1,1-trichloroethane was demonstrated in reaction mixtures containing rat nuclei cytochrome P-450 preparations (Casciola and Ivanetich 1984).

In vivo and *in vitro* evidence from rat experiments suggests that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated, to a limited extent, to dechlorinated

FIGURE 2-3. Metabolic Scheme for 1,1,1-Trichloroethane



radical intermediates and eventually to acetylene (Durk et al. 1992); in these experiments, exhaled acetylene accounted for <1% of metabolized 1,1,1-trichloroethane. The reductive dechlorination of 1,1,1-trichloroethane appears to be mediated by cytochrome P-450, since putative induction by phenobarbital treatment accelerated the *in vitro* and *in vivo* metabolic formation of acetylene. The reductive metabolic pathway is not indicated in Figure 2-3, because it apparently represents a very minor 1,1,1-trichloroethane metabolic pathway.

Repeated exposure of mice and rats to 1,1,1-trichloroethane apparently does not increase the relative importance of metabolism to the *in vivo* disposition of the compound (Schumann et al. 1982b), even though another research group reported that hepatic microsomes from rats exposed continuously for 10 days to 800 ppm of 1,1,1-trichloroethane displayed greater *in vitro* enzymatic activities for 1,1,1-trichloroethane oxidation than microsomes from fresh-air controls (Koizumi et al. 1983). Schumann et al. (1982b) found that repeated exposure of rats or mice to 1,500 ppm unlabeled 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, the extent of metabolism, or the concentration of radioactivity in tissues after a 6-hour inhalation exposure to 1,500 ppm [2-^{14}C]-1,1,1-trichloroethane, compared with age-matched animals subjected to single 6-hour exposures. In general, studies regarding the effects of 1,1,1-trichloroethane on hepatic cytochrome P-450 enzyme levels are inconclusive. Although Koizumi et al. (1983) and others (Fuller et al. 1970; La1 and Shah 1970) reported that 1,1,1-trichloroethane induced hepatic cytochrome P-450 enzyme levels in rats, others observed no effects (Toftgaard et al. 1981) or inhibitory ,effects (Savolainen et al. 1977) in rats exposed to 1,1,1-trichloroethane.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

After acute exposure, most inhaled 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60-80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Other humans exposed to 35 or 350 ppm for 6 hours exhaled >91% of absorbed 1,1,1-trichloroethane as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Similar observations were made in studies

of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982a, 1982b), mice (Schumann et al. 1982a, 1982b), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment.

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane. Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Seki et al. 1975). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10-27 hours for trichloroethanol and 70-85 hours for trichloroacetic acid (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982a, 1982b; Takahara 1986a).

2.3.4.2 Oral Exposure

Humans eliminate ingested 1,1,1-trichloroethane in their exhaled breath (Stewart and Andrews 1966), but no studies were located that quantified excretion rates or the extent of excretion. The pattern of elimination is expected to be similar to that of inhaled 1,1,1-trichloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes). This pattern has been observed in animals after inhalation (see Section 2.3.4.1) and oral exposure (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987). In rats exposed to 1,1,1-trichloroethane in drinking water for 8 hours (total dose of 116 mg/kg), the primary route of excretion was rapid elimination of unchanged 1,1,1-trichloroethane in

expired air; only 3% of the ingested dose was metabolized (Reitz et al. 1988). Essentially all of the ingested 1,1,1-trichloroethane was excreted within 30 hours. Similar results were obtained in gavage studies with rats and mice (Mitoma et al. 1985; RTI 1987).

2.3.4.3 Dermal Exposure

The pattern of excretion in humans after dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloroethane: rapid exhalation of 1,1,1-trichloroethane in expired air is the major excretion route; exhalation of CO_2 and urinary excretion of other metabolites are minor routes (see Section 2.3.4.1). Several studies have measured 1,1,1-trichloroethane in the expired breath of humans after (and during) short-term dermal exposure to 1,1,1-trichloroethane (Fukabori et al. 1977; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964), but 1,1,1-trichloroethane exhalation as a percentage of absorbed dose was not quantitated in these studies.

2.3.4.4 Other Routes of Exposure

Results in animals given 1,1,1-trichloroethane injections indicate that excretion patterns in animals are similar regardless of route. In mice given intraperitoneal injections of 1,1,1-trichloroethane, 88% of the dose was excreted unchanged in expired air, and 1% was excreted as metabolites in urine (Takahara 1986b). In rats given intraperitoneal injections, 98.7% of the dose was exhaled as unchanged 1,1,1-trichloroethane (Hake et al. 1960). Within 24 hours of intravenous injection of radiolabeled 1,1,1-trichloroethane, exhalation of radioactivity accounted for 91 and 80% of the administered doses in rats and mice, respectively; only trace amounts of radioactivity remained in the tissues after 24 hours (RTI 1987). In dogs, 60-70% of intravenously injected 1,1,1-trichloroethane was excreted in expired air within 1 hour (Hobara et al. 1981).

2.3.5 Mechanisms of Action

1,1,1-Trichloroethane is rapidly and extensively absorbed from the lungs (Astrand et al. 1973; Dallas et al. 1989; Hobara et al. 1982, 1983; Monster et al. 1979; Morgan et al. 1972a, 1972b; Nolan et al. 1984), the skin (Fukabori et al. 1977; Morgan et al. 1991; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964; Tsuruta 1975) and the gastrointestinal tract (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). The lipophilic nature of 1,1,1-trichloroethane, the rates of

absorption upon various routes of exposure, and the rates at which the chemical leaves the body in expired air when exposure is terminated all suggest that 1,1,1-trichloroethane is very likely transported across cellular membranes by passive diffusion.

No known specific intermediary molecules influence the distribution of 1,1,1-trichloroethane among tissues in the body. The lipophilicity and volatility of 1,1,1-trichloroethane, along with the low rates at which it is metabolized, appear to be the most important factors influencing distribution within and elimination from the body. The compound is widely distributed by the blood among tissues, with preferential accumulation in fatty tissues, and is rapidly cleared following exposure cessation (Holmberg et al. 1977; RTI 1987; Schumann et al. 1982a, 1982b; Takahara 1986b).

The mechanism by which high levels of 1,1,1-trichloroethane produces mild to moderate hepatotoxic effects in humans and animals is only partially understood. Studies of more potent hepatotoxic chlorinated alkanes (including carbon tetrachloride, chloroform, and 1,1,1-trichloroethane) have clearly demonstrated an involvement of cytochrome P-450-mediated dechlorination in the production of liver injury (Plaa 1986). It has been hypothesized that the production of free radicals via the homolytic cleavage of the carbon-chlorine bond in these hepatotoxic chlorinated alkanes occurs in the endoplasmic reticulum of hepatocytes, and that the free radicals react with unsaturated lipids and proteins in the endoplasmic reticulum, producing lipid peroxidation and covalent binding. These actions lead to morphological and functional changes in this organelle and, eventually, to cellular dysfunction (triglyceride accumulation) and necrosis (Plaa 1986). The potency of the 1,1,2- isomer of trichloroethane to produce liver injury is markedly greater than that of the 1,1,1- isomer (Carlson 1973; Takahara 1986~). This difference has been associated with differences in the metabolic activation of the two isomers. 1,1,2-Trichloroethane is metabolized to a much greater extent in mice and rats after gavage administration than is 1,1,1-trichloroethane. Urinary excretion of metabolites accounted for >70% of the administered doses of the 1,1,2- isomer; in contrast, >85% of the administered 1,1,1- isomer dose was excreted unchanged in expired air (Mitoma et al. 1985). In experiments with rat liver microsomes, Van Dyke and Wineman (1971) observed that 9.8% of the chloride was enzymatically removed from the 1,1,2- isomer, compared with <0.5% removal of chloride from the 1,1,1- isomer in the same period. The difference in extent of metabolism of the 1,1,2- and 1,1,1- isomers explains the difference in hepatotoxicity of the two compounds (i.e., the 1,1,2- isomer is more potent because greater quantities of reactive metabolites are produced from it); however, whether the mild hepatotoxicity of 1,1,1-trichloroethane is mediated by a metabolite or by the compound itself

is unclear. Carlson (1973) reported that rats pretreated with phenobarbital displayed signs of liver injury (increased levels of SGPT and SGOT and decreased activity of glucose-6-phosphatase) immediately following a 2-hour exposure to 11,600 ppm 1,1,1-trichloroethane; these signs were not apparent in nonpretreated rats exposed to the same 1,1,1-trichloroethane concentration or in rats that had received only the phenobarbital pretreatment. This suggests that metabolic activation is involved in the expression of 1,1,1-trichloroethane's hepatotoxicity. Another study, however, did not find that phenobarbital pretreatment potentiated the hepatotoxicity of 1,1,1-trichloroethane (Cornish et al. 1973).

Acute exposures to high 1,1,1-trichloroethane concentrations can cause sudden death in humans due to ventricular fibrillation, myocardial depression, or respiratory arrest. Animal studies show that arrhythmias (that can lead to ventricular fibrillation) can be produced by exogenously administered epinephrine during or immediately after inhalation exposure to 1,1,1-trichloroethane (Carlson 198 1; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). 1,1,1-Trichloroethane is one of the most potent arrhythmogenic of the volatile organic compounds. The studies indicate that the arrhythmias are not caused directly by 1,1,1-trichloroethane, but result from its sensitization of the heart to epinephrine. The basis for the sensitization is not completely understood, but evidence suggests that the sensitization is produced by 1,1,1-trichloroethane itself and not by its metabolites. Carlson (1981) reported that pretreatment of rabbits with phenobarbital (thereby increasing 1,1,1-trichloroethane metabolism) did not increase the incidence of epinephrine-induced arrhythmias during l-hour exposures to 5,600 ppm, and that treatment with cytochrome P-450 inhibitors (SKP-525A and Lilly 18947) (decreasing the metabolism of 1,1,1-trichloroethane) 30 minutes before exposure to 1,1,1-trichloroethane increased the incidence of epinephrine-induced cardiac arrhythmias. The arrhythmogenicity of 1,1,1-trichloroethane and other halogenated hydrocarbons may involve intercellular communication inhibition, presumably through parent-compound modification of gap junctions between cardiac myocytes. Toraason et al. (1992) demonstrated that a series of halogenated hydrocarbons, including 1,1,1-trichloroethane, inhibited the transfer of a fluorescent probe between adjacent cultured cardiac myocytes isolated from neonatal rats (an assay for gap junction communication) and that the inhibition was not affected by pretreating the cells with SKF-525A. Toraason et al. (1992) noted that the ability of the compounds to inhibit intercellular communication paralleled their ability to sensitize the heart to epinephrine-induced arrhythmias.

Acute exposure to high concentrations of 1,1,1-trichloroethane (≈10,00-26,000 ppm) lowered blood pressure in humans and animals within minutes of exposure (Herd et al. 1974; Kobayashi et al. 1988;

McLeod et al. 1987; Wright and Strobl 1984). Studies with anesthetized dogs associated the decrease in blood pressure with peripheral vasodilation at the lower end of the effective concentration range and with decreased heart rate and myocardial contractility at higher concentrations (Herd et al. 1974; Kobayashi et al. 1988). Intravenous administration of phenylephrine (an agent that putatively constricts peripheral vasculature) or calcium counteracted the blood pressure-reducing effects of 1,1,1-trichloroethane in anesthetized dogs (Herd et al. 1974). Herd et al. (1974) hypothesized that 1,1,1-trichloroethane, because of its lipophilic nature, may produce cardiotoxic effects through an interference with membrane-dependent processes such as adenosine triphosphate (ATP) production by cardiac mitochondria and calcium mobilization during myocardial contraction. More recently, Toraason et al. (1990) demonstrated a reversible, concentration-dependent inhibitory effect of 1,1,1-trichloroethane on the contractility (i.e., decreased beating frequency) of cultured rat heart cells. Hoffman et al. (1992) showed that 1,1,1-trichloroethane inhibits calcium mobilization during excitation-contraction coupling in isolated ventricular myocytes from rat neonates, and hypothesized that myocardial depression following exposure to 1,1,1-trichloroethane results from reduced intracellular calcium concentration during systole.

Respiratory arrest due to central nervous system depression has been proposed as a possible explanation for sudden deaths following acute exposure to high concentrations of 1,1,1-trichloroethane (Adams et al. 1950; Jones and Winter 1983; Torkelson et al. 1958). In general, the actions of 1,1,1-trichloroethane are very similar to other central nervous system depressants. The mechanism by which acute exposures to high concentrations of 1,1,1-trichloroethane depress the central nervous system is poorly understood, but is thought to involve interactions or the mere presence of the compound with lipids and/or proteins in neural membranes that lead to dysfunction (Evans and Balster 1991). In support of the hypothesis that the central nervous system depressive effect of 1,1,1-trichloroethane and other organic solvents may be due to interactions with proteinaceous components of membranes, Korpela (1989) demonstrated that 1,1,1-trichloroethane (and other organic solvents) inhibited the activities of membrane-bound integral enzymes (acetylcholinesterase and magnesium-activated ATPase) in synaptosomes isolated from rat cerebrum.

2.4 RELEVANCE TO PUBLIC HEALTH

Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Deaths of persons exposed to high concentrations have been attributed to cardiac arrhythmia and respiratory failure secondary to central nervous system depression. Mild developmental effects observed in animals at high levels have not been verified in humans. Animal studies suggest that exposure to 1,1,1-trichloroethane is not likely to cause reproductive effects or cancer. In general, route of exposure does not appear to be as important as circulating levels of 1,1,1-trichloroethane. Overall, it does not appear that exposures likely to occur near NPL hazardous waste sites are likely to have a deleterious effect on the public's health.

Minimal Risk Levels for 1,1,1-Trichloroethane

Inhalation MRLs

- An MRL of 2 ppm has been derived for acute inhalation exposure (14 days or less) to 1,1,1-trichloroethane.

The acute inhalation MRL is based on a LOAEL of 175 ppm for reduced performance of psychomotor tests in a human study by Mackay et al. (1987). Individuals exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours demonstrated impaired performance of psychomotor tests. The derivation of this MRL is supported by the study results of Gamberale and Hultengren (1973), who also found psychophysiological test performance deficits in exposed individuals, although at a higher concentration, and by numerous studies showing behavioral and neurophysiological effects in animals.

- An MRL of 0.7 ppm has been derived for intermediate inhalation exposure (15-364 days) to 1,1,1-trichloroethane.

The intermediate inhalation MRL is based on a NOAEL of 70 ppm derived from the study by Rosengren et al. (1985) which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months. Choice of a neurological end point for derivation of the MRL is supported

by numerous studies in humans and animals showing neurological effects to be the critical end point for 1,1,1-trichloroethane.

A chronic inhalation MRL was not derived because suitable studies including tests for subtle neurological effects were not available.

Oral MRLs

Oral MRLs were not derived for 1,1,1-trichloroethane due to the lack of adequate studies. Unpublished studies by Bruckner (1983), which were initially considered as potential candidates for derivation of acute- and intermediate-duration oral MRLs, were peer-reviewed and found to be of inadequate design. A similar conclusion was found regarding a chronic-duration oral study by Maltoni et al. (1986).

Death. The volatility of 1,1,1-trichloroethane, in addition to the rapid and extensive absorption and elimination of the inhaled compound, makes acute inhalation in product use situations the most likely lethal exposure scenario in humans. The acute lethal air concentration for humans is unknown; however, simulations of several lethal exposures suggest that it may be as low as 6,000 ppm (Droz et al. 1982; Jones and Winter 1983; Silverstein 1983). The results of animal studies indicate that the acute lethal exposure concentration decreases substantially with increasing exposure duration. Thus, the concentration required to cause animal death after a 6-7-hour exposure is 3-4 times less than that required after a 15-minute exposure (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982; Gradiski et al. 1978).

Human deaths after inhalation exposure to 1,1,1-trichloroethane have been attributed to respiratory failure secondary to central nervous system depression and to cardiac arrhythmias (Guberan et al. 1976; Hall and Hine 1966; Jones and Winter 1983; MacDougaJl et al. 1987; Stahl et al. 1969; Travers 1974). Animal studies reveal that arrhythmias may result from sensitization of the heart to epinephrine (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973). Hypoxia may exacerbate the situation (Reinhardt et al. 1971). Therefore, acute lethal exposure levels may be lower in individuals exposed during physical exertion (King et al. 1985; Ranson and Berry 1986; Troutman 1988). Physical exertion also may decrease the acute lethal exposure level by increasing the respiratory rate and lung perfusion rate, thereby increasing the systemic absorption of 1,1,1-trichloroethane.

Very little is known about the lethality of ingested 1,1,1-trichloroethane in humans. In one case of acute oral exposure, accidental ingestion of 600 mg/kg of 1,1,1-trichloroethane was not fatal (Stewart and Andrews 1966). Animal studies suggest that even higher acute oral doses may not cause death. (Kinkead and Wolfe 1992; Torkelson et al. 1958).

Human deaths involving dermal exposure to 1,1,1-trichloroethane have not been reported. Such an occurrence is extremely unlikely in view of the high volatility of 1,1,1-trichloroethane, which would limit the amount of 1,1,1-trichloroethane in contact with the skin, and the relatively slow rate of percutaneous absorption. Animal deaths were observed only when extremely high doses (15,800 mg/kg) were applied to the skin for prolonged periods (e.g., 24 hours) under occlusive dressings (Torkelson et al. 1958).

Systemic Effects.

Respiratory Effects. Respiratory depression produced by 1,1,1-trichloroethane is considered secondary to central nervous system depression. See the discussion of Neurological Effects for more information.

Cardiovascular Effects. 1,1,1-Trichloroethane can lower blood pressure (mildly to severely) in humans (Domette and Jones 1960; Krantz et al. 1959) and can induce transient myocardial injury (Wodka and Jeong 1991). Such effects, however, are likely only after exposure to very high concentrations of 1,1,1-trichloroethane vapor. Daily exposure to low levels for 16 years did not affect blood pressure, heart rate, or electrocardiogram results in humans (Kramer et al. 1978). Reduced blood pressure accompanies exposure to anesthetic concentrations of 1,1,1-trichloroethane vapor (10,000-26,000 ppm). The effects are not permanent and subside shortly after exposure. The hypotensive mechanism has been studied in animals and appears to involve cardiac depression and peripheral vasodilation (Herd et al. 1974).

Human deaths following 1,1,1-trichloroethane inhalation are often attributed to cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Such conclusions are based on animal studies in which arrhythmias have been produced during or immediately following acute inhalation exposure to 1,1,1-trichloroethane (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The mechanism for the arrhythmias apparently involves sensitization of the heart to endogenous epinephrine. The exposure level at which cardiac sensitization occurs in

humans is not known, but in animals, concentrations as low as 5,000 ppm are effective after only 10 minutes of inhalation (Reinhardt et al. 1973). Physical exertion, stress, or any other stimulus of epinephrine release from the adrenal medulla may render an individual more vulnerable to 1,1,1-trichloroethane. Hypoxia may further increase a subject's susceptibility.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea reportedly occur in humans after acute oral or inhalation exposure to high 1,1,1-trichloroethane levels (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971; Stewart and Andrews 1966). Vomiting and diarrhea have not been reported in animals (rodents, the most commonly used laboratory animals, cannot vomit). The mechanisms for these effects are not known.

Hepatic Effects. 1,1,1-Trichloroethane may be a mild hepatotoxin in humans, although the evidence is not conclusive. Increased levels of serum bilirubin, LDH, alkaline phosphatase and SGOT, all suggestive of liver injury, have been reported in humans exposed to high levels of 1,1,1-trichloroethane by inhalation or ingestion (Halevy et al. 1980; Hodgson et al. 1989; Stewart and Andrews 1966). Mild hepatic changes have also been found by liver biopsy in exposed individuals and at autopsy in individuals who died after acute inhalation exposure to high concentrations of 1,1,1-trichloroethane (Caplan et al. 1976; Halevy et al. 1980; Hall and Hine 1966; Hodgson et al. 1989). Animals studies indicate that exposure to relatively high 1 ,l ,l -trichloroethane concentrations in air (≥1,000 ppm) or high oral doses (≥1,334 mg/kg) are required to produce liver injury (Adams et al. 19.50; Bruckner 1983; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958; Tyson et al. 1983). Effects observed in animals include necrosis, fatty change, increased liver weight, and changes in liver and serum enzyme levels. These effects are reversible and subside after termination of exposure (in the case of necrosis, hepatocytes in the proximity of the killed cells proliferate and replace them).

Dermal Effects. 1,1,1-Trichloroethane is mildly irritating when applied undiluted to the skin for extended periods (Duprat et al. 1976; Stewart and Dodd 1964; Torkelson et al. 1958; Wahlberg 1984a, 1984b). Effects include slight, transient, reversible erythema and edema. Low concentrations in water, however, are not likely to cause skin irritation when bathing or showering.

Ocular Effects- Exposure to high levels of 1,1,1-trichloroethane vapor is associated with mild eye irritation in humans (Stewart et al. 1961) and mice (Evans and Balster 1993). Tests in animals suggest

that 1 ,l ,l -trichloroethane applied directly to the eye is likely to cause only mild eye irritation in humans (Duprat et al. 1976; Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958).

Immunological and Lymphoreticular Effects. Immunological effects of 1,1,1-trichloroethane have not been reported in humans, other than one case of dermal sensitization (Ingber 1991) and have not been studied extensively in animals. Spleen congestion has been observed in subjects who were accidentally exposed to 1,1,1-trichloroethane at a high concentration (Gresham and Treip 1983; Stahl et al. 1969); however, this effect may have been due to altered peripheral hemodynamics. Acute inhalation exposure had no effect on survival from a bacterial pathogen challenge in mice (Aranyi et al. 1986). Histological evaluation of lymphoreticular tissues from rats and mice (including lymph nodes, thymus, and spleen) have not revealed any lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Comish and Adefuin 1966; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958); however, more extensive immune function studies would be required to adequately evaluate the immunotoxic potential of 1,1,1-trichloroethane in humans.

Neurological Effects. Neurological effects are the preeminent signs of acute inhalation exposure to 1,1,1-trichloroethane in humans. The intoxicating effects of the inhaled chemical create a potential for its abuse. The severity of CNS depressant effects in humans during acute inhalation exposure increases as the exposure duration and level are increased. Impaired performance of psychophysiological function tests has been observed in individuals exposed to moderate concentrations (≥175 ppm) (Gamberale and Hultengren 1973; Mackay et al. 1987). The Mackay et al. (1987) study served as the basis for the acute-duration inhalation MRL. Dizziness, lightheadedness, and loss of coordination are caused by exposure to higher concentrations (>500 ppm) (Stewart et al. 1961, 1969; Torkelson et al. 1958). General anesthesia occurs at high levels (≥10,000 ppm) (Domette and Jones 1960). These effects subside rapidly after exposure. A recent report suggested that impaired memory and deficits in balance were persistent effects in a group of workers after chronic exposure to moderate to high levels of 1,1,1-trichloroethane (Kelafant et al. 1994). This population is being followed-up to determine the validity of these new findings.

Animals are useful models for examining the neurological effects of exposure to 1,1,1-trichloroethane. As in humans, central nervous system depression is the predominant effect of inhaled 1,1,1-trichloroethane. Signs include ataxia, unconsciousness, and death at increasing concentrations (Bonnet et al.

1980; Clark and Tinston 1982; Evans and Balster 1993; Gehring 1968; Hougaard et al. 1984; Lazarew 1929). No evidence of gross or histological damage was found in the brains of most exposed animals, but lasting physical changes in the brain are indicated by reports of increased levels of glial fibrillary acid protein and decreased DNA content in the brain of gerbils after intermediate exposure to low levels of the chemical (Karlsson et al. 1987; Rosengren et al. 1985). The Rosengren et al. (1985) study served as the basis for the intermediate-duration inhalation MRL. Alterations of brain metabolism also were observed in exposed animals (Folbergrova et al. 1984; Hougaard et al. 1984; Nilsson 1986a, 1986b). Behavioral changes, including impaired performance of neurobehavioral tests and increased motor activity, have been widely reported (Albee et al. 1990a; Balster et al. 1982; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a; Mattsson et al. 1993; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Woolverton and Balster 1981); however, the sites of action and biochemical mechanisms of neurotoxicity have not been identified. Neurophysiological changes also have been reported (Albee et al. 1990b). These latter observations were made at relatively high exposure levels.

Little information was located regarding neurological effects in humans or animals after oral or dermal exposure to 1,1,1-trichloroethane. Existing data indicate that a single oral exposure to a dose of approximately 600 mg/kg did not produce overt signs of neurotoxicity (Stewart and Andrews 1966). It is assumed, however, that sufficiently high doses of 1,1,1-trichloroethane administered orally or dermally will result in neurological effects. Oral exposure to 1,1,1-trichloroethane produced neurophysiological changes in rats given moderate doses (700 mg/kg/day) (Spencer et al. 1990), and in gross neurobehavioral changes (hyperexcitability and narcosis) in rats given high doses (5,000 mg/kg/day) (Bruckner 1983). No neurological effects were observed in the offspring of rats treated by gavage during gestation and lactation with up to 750 mg 1,1,1-trichloroethane/kg/day (Dow Chemical 1993) (see Developmental Effects).

Reproductive Effects. Adverse effects of 1,1,1-trichloroethane on reproduction in humans have not been reported. Taskinen et al. (1989) found no relationship between adverse pregnancy outcomes and exposure of fathers to 1 ,l ,l-trichloroethane during spermatogenesis. Histological evaluation of reproductive organs and tissues from rats and mice of either sex revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was

observed in guinea pigs (Adams et al. 1950). More extensive and sensitive tests are required before the potential for human reproductive effects can be fully evaluated.

Developmental Effects. Developmental effects in humans exposed to 1,1,1-trichloroethane have not been observed. Epidemiology studies found no relationship between adverse pregnancy outcomes and maternal exposure to 1,1,1-trichloroethane (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane (BRRC 1987a, 1987b; York et al. 1982). Effects included decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. The developmental defects reported in two of these studies (BRRC 1987a, 1987b) may have been associated with significant maternal toxicity. Neither an inhalation study using a lower, although still high, concentration (Schwetz et al. 1975) nor drinking water studies (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b) revealed any developmental effects. Furthermore, a recent comprehensive study in which pregnant rats were gavaged with 1,1,1-trichloroethane during gestation and lactation found no neurobehavioral alterations in the pups tested up to 2 months of age (Dow Chemical 1993). Overall, 1,1,1-trichloroethane does not appear to be a significant developmental toxicant in animals. However, in view of the known neurological effects of 1,1,1-trichloroethane in humans and animals, additional developmental studies that examine neurological end points would be an important component of a complete investigation of 1,1,1-trichloroethane's potential developmental toxicity in humans.

Genotoxic Effects. The genotoxic effects of 1,1,1-trichloroethane have been studied ,extensively . The results are summarized in Tables 2-4 and 2-5. Although most tests of mutagenicity in the Ames *Salmonella* assay produced negative results, those conducted in a desiccator, to minimize evaporation and maximize exposure, were mostly positive (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results indicate that 1,1,1-trichloroethane may be mutagenic in *Salmonella. The* results were negative in other tests of genotoxicity in bacteria and fungi. 1,1,1-Trichloroethane is a relatively volatile compound; therefore, a high evaporation rate could result in lower doses reaching the microorganisms and thus affect the outcome of genotoxicity tests. This explanation may account for the largely negative results observed in tests with bacteria and fungi. On the other hand, many compounds more volatile than 1,1,1-trichloroethane are positive in these studies.

TABLE 2-4. Genotoxicity of 1,1,1-Trichloroethane *In Vivo*

Species (test system)	End point	Results	Reference
Tradescantia	Pigmentation change in plant stamen hairs	+	Schairer et al. 1983
Drosophila melanogaster	Sex linked recessive lethal mutations	–	Gocke et al. 1981
Mouse erythrocytes	Micronucleus test	–	Tsuchimoto and Matter 1981
Mouse bone marrow	Micronucleus test	–	Gocke et al. 1981; Katz et al. 1981; Mackay 1990; Salamone et al. 1981
Mouse liver	DNA adducts	(+)	Turina et al. 1986
Mouse liver	DNA unwinding	–	Taningher et al. 1991

– = negative; + = positive; (+) = weakly positive; DNA = deoxyribonucleic acid

TABLE 2-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium on plates	Reverse mutation	–	–	Baker and Bonin 1981; Brooks and Dean 1981; Ichinotsubo et al. 1981; MacDonald 1981; Martire et al. 1981; Mersch-Sundermann 1989; Nagao and Takahashi 1981; Nestmann et al. 1980; Quillardet et al. 1985; Richold and Jones 1981; Rowland and Severn 1981; Simmon and Shepherd 1981; Trueman 1981; Venitt and Crofton-Sleigh 1981
S. typhimurium in liquid	Reverse mutation	–	–	Falck et al. 1985; Suovaniemi et al. 1985
S. typhimurium on plates in dessicator	Reverse mutation	+	+	Nestmann et al. 1980, 1984; Gocke et al. 1981; Simmon et al. 1977
		–	–	Milman et al. 1988
S. typhimurium	Fluctuation	–	–	Gatehouse 1981; Hubbard et al. 1981
S. typhimurium	Forward mutation	–	No data	Skopek et al. 1981
		–	–	Roldan-Arjona et al. 1991
S. typhimurium	*umu*-test	–	–	Nakamura et al. 1987; Ono et al. 1991a, 1991b
	Rec-assay for DNA repair	–	–	Kada 1981
Escherichia coli	Reverse mutation	–	–	Matsushima et al. 1981
E. coli	Differential killing	–	–	Green 1981; Tweats 1981
E. coli	Lambda prophage induction	–	–	Thomson 1981
E. coli	Gene induction	–	No data	Quillardet et al. 1985
E. coli	Growth inhibition	(+)	–	Rosenkranz et al. 1981

TABLE 2-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Eukaryotic organisms:				
Fungi:				
Schizosaccharomyces pombe	Forward mutation	–	–	Loprieno 1981
Aspergillus nidulans	Forward mutation	No data	–	Crebelli and Carere 1987
A. nidulans	Mitotic aneuploidy	No data	–	Cerebelli and Carere 1987; Crebelli et al. 1988
A. nidulans	Mitotic crossing over	No data	–	Crebelli and Carere 1987
Saccharomyces cerevisiae	Reversion	–	–	Mehta and von Borstel 1981
S. cerevisiae	Mitotic aneuploidy	No data	–	Whittaker et al. 1990
		–	No data	Parry and Sharp 1981
S. cerevisiae	Mitotic crossing over	–	–	Kassinova et al. 1981
S. cerevisiae	DNA repair	–	–	Sharp and Parry 1981a
S. cerevisiae	Mitotic gene conversion	–	–	Sharp and Parry 1981b; Jagannath et al. 1981; Zimmerman and Scheel 1981
Mammalian cells:				
HeLa cells	Unscheduled DNA synthesis	–	–	Martin and McDermid 1981
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Milman et al. 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	–	Althaus et al. 1982; Milman et al.1988; Shimada et al. 1985; Williams et al. 1989

TABLE 2-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat hepatocytes	Degranulation of endoplasmic reticulum	No data	+	Fey et al. 1981
Human lymphoblasts	Gene locus mutation	No data	–	Penman and Crespi 1987
L5178Y mouse lymphoma cells	Forward mutation	?	–	Myhr and Caspary 1988
		–	–	Mitchell et al. 1988
Chinese hamster ovary cells	Chromosome aberrations	(+)	+	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	–		Perry and Thomson 1981
		?	–	Galloway et al. 1987
Human peripheral lymphocytes	Sister chromatid exchange	No data	–	Lindahl-Kiessling et al. 1989
Baby hamster kidney cells	Cell transformation	–	No data	Styles 1981
		+	+	Daniel and Dehnel 1981
Rat embryo cells F1706	Cell transformation	No data	+	Price et al. 1978
Hamster embryo cells	Cell transformation	No data	+	Hatch et al. 1982, 1983
Mice BALB/c-3T3 cells	Cell transformation	No data	+	Tu et al. 1985; Milman et al. 1988
Calf thymus	Binding to DNA	–	No data	DiRenzo et al. 1982

– = negative; + = positive; (+) = weakly positive; ? = equivocal; DNA = deoxyribonucleic acid

Most assays of genotoxicity in mammalian cells have been negative, but 1,1,1-trichloroethane did produce chromosomal aberrations in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987). *In vivo* micronucleus tests for chromosomal aberrations were all negative (Gocke et al. 1981; Katz et al. 1981; Mackay 1990; Salamone et al. 1981; Tsuchimoto and Matter 1981). Positive or weakly positive results were reported in assays for unscheduled DNA synthesis in mouse hepatocytes (Milman et al. 1988); degranulation of endoplasmic reticulum, which measures the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes *in vitro* (Fey et al. 1981); and formation of DNA adducts (binding of the compound to DNA) in mouse liver *in vivo* (Turina et al. 1986). Tests of cell transformation in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells were almost all positive (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Cell transformation systems are believed to be similar to the process of neoplastic transformations.

Although 1,1,1-trichloroethane was mutagenic in a few assays with *Salmonella,* induced chromosomal aberrations in a Chinese hamster ovary cell assay, and was positive in most mammalian cell transformation assays, the existing genotoxicity data are largely negative. In addition, positive results may have been produced by stabilizers and not 1,1,1-trichloroethane itself. Therefore, a firm conclusion regarding the genotoxic potential of 1,1,1-trichloroethane in humans is not possible.

Cancer. A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Among animals, no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988). The results of an oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats; however, the biological and statistical significance of these results are questionable because of the study design limitations (Maltoni et al. 1986). The results of another oral (gavage) cancer bioassay (NCI 1977) were negative, but high early mortality in treated animals in this study made these results questionable.

Information is also limited on the role of 1,1,1-trichloroethane metabolites in the compound's toxicity. Reactive metabolites are important in the carcinogenicity of other chloroethanes (i.e., 1,1,2,2-tetrachloroethane). Binding to DNA, which is correlated with carcinogenicity in chlorinated ethanes (Lattanzi et al. 1988), was weak in an *in vivo* test (Turina et al. 1986). Even weak binding, however, indicates the potential to interact with DNA. Cell biotransformation tests were positive for

this chemical (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). The results of these assays may have been confounded by the presence of stabilizing agents, however. Two of the common stabilizing additives in commercial formulations of 1,1,1-trichloroethane are 1,2-epoxybutane (butylene oxide), and 1,4-dioxane (diethylene dioxide). Both stabilizers have been identified as animal carcinogens (NTP 1989a). At this time, it does not appear that 1,1,1-trichloroethane exposure poses a clear cancer risk in animals; however, as discussed above, the limitations of the available studies prevent a definitive assessment of the risk of cancer in humans exposed to the compound. Related to potential exposures near NPL hazardous waste sites, the risk appears to be of little significance.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,1,1-trichloroethane are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals

of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,1-trichloroethane are discussed in Section 2.5.2.

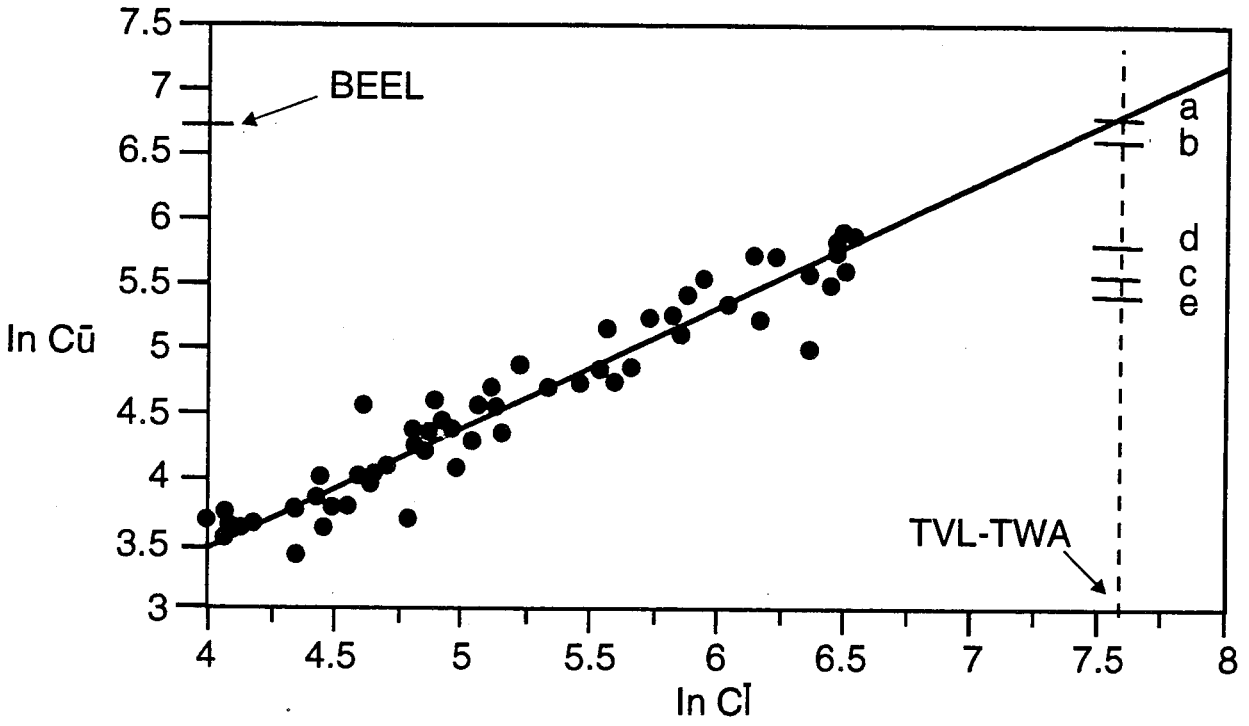
A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to 1,1,1-Trichloroethane

Environmental levels of 1,1,1-trichloroethane have been correlated with levels in expired air, blood, and urine. After extensive studies, a significant correlation was observed between the environmental exposure of humans to 1,1,1-trichloroethane and levels of the chemical in expired air in various United States locations during various seasons (Hartwell et al. 1987a; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). Levels of 1,1,1-trichloroethane and its metabolites, trichloroethanol and trichloroacetic acid, have been quantified in the blood, expired air, and urine of workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week (Monster 1986). Immediately following exposure, urine levels of trichloroethane and trichloroacetic acid were 4.9 and 2.5 mg/g creatinine, respectively. At 5-15 minutes after exposure, 1,1,1-trichloroethane levels in the blood and expired air were 0.9 mg/L and 210 mg/m^3, respectively. The blood levels of trichloroethanol and trichloroacetic acid were 0.16 and 2.3 mg/L, respectively. For comparison, the baseline level of 1,1,1-trichloroethane in the blood of unexposed, normal subjects was 0.0002 mg/L (range <0.0001-0.0034 mg/L), and the blood level of trichloroacetic acid was 0.0214 mg/L (Hajimiragha et al. 1986).

Studies of 1,1,1-trichloroethane levels in expired air or its metabolites in the urine have established a linear correlation between urinary trichloroethanol concentrations and environmental 1,1,1-trichloroethane levels or 1,1,1-trichloroethane levels absorbed through the lungs (Ghittori et al. 1987; Imbriani et al. 1988; Monster 1986; Pezzagno et al. 1986; Seki et al. 1975; Stewart et al. 1961). Data from Imbriani et al. (1988) are presented in Figure 2-4. Monster (1986) proposed that the best method for

Figure 2-4. Scatter Diagram Relating Time-Weighted Average of Environmental Concentration and Urinary Concentration of 1,1,1-Trichloroethane in Exposed Workers



Scatter diagram relating the time-weighted average of the environmental concentration (in the breathing zone) (C̄I) and the urinary concentration (Cū) of 1,1,1-trichloroethane in the exposed workers (experiment II). The regression line (Cū=0.45xCI+12.6; r=0.95; N=60) is also drawn.
a Cū value at C̄I = 1,900 mg/m^3 (TLV-TWA)
b 95% lower confidence limit = biological exposure limit
c hypothetical value of Cū in an occupationally exposed subject
d one-sided upper confidence limit (at 95%) of Cū
e one-sided lower confidence limit (at 95%) of Cū

Classification system:
1 d<b (or d/b<1) = compliance exposure
2 e>b (or e/b>1) = noncompliance exposure
3 any individual which cannot be classified in 1 or 2 = possible overexposure

The C̄I and Cū values are shown as 1n numbers to allow all the data in a same diagram. The TVL-TWA is 19,900 mg/m^3 (anti-1n 7.549).
The BEEL is 805 μ/L (anti-1n 6.690)

Taken from Imbriani et al. 1988

estimating occupational exposure to I ,l,l-trichloroethane was to determine the levels of 1,1,1-trichloroethane and trichloroacetic acid in blood after work on Fridays.

The length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-trichloroethane is rapidly eliminated from the body; ≥99% is eliminated within 50 hours (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). See Section 2.3 for more information regarding the pharmacokinetics of 1,1,1-trichloroethane. The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,1,1-Trichloroethane

The central, nervous system is apparently the most sensitive tissue to 1,1,1-trichloroethane exposure. Decreased psychomotor performance, altered EEG recordings, ataxia, and anesthesia have been observed in humans after acute exposure (Domette and Jones 1960; Mackay et al. 1987; Stewart et al. 1975; Torkelson et al. 1958). Mild hepatic effects and decreased blood pressure have also been noted (Domette and Jones 1960; Stewart et al. 1961). Numerous animal studies provide supporting evidence for the sensitivity of the central nervous system to acute and intermediate-duration exposure to 1,1,1-trichloroethane. Adverse cardiovascular effects and mild hepatic effects have also been observed in animals. Indices of central nervous system, hepatic, and cardiovascular effects are of limited value, as biomarkers, since many other lipophilic chemicals (including some likely to be present at the same sites as 1,1,1-trichloroethane) may cause similar effects in these target organs.

No specific biomarkers of effects caused by 1,1,1-trichloroethane were found in the literature. Additional information regarding the effects of exposure to 1,1,1-trichloroethane can be found in OTA (1990) and CDC/ATSDR (1990). For a more detailed discussion of the health effects caused by 1,1,1-trichloroethane see Section 2.2 of Chapter 2.

2.6 INTERACTIONS WITH OTHER SUBSTANCES

Although there are no reports of chemical interactions in humans, several animal studies have identified possible interactions between 1,1,1-trichloroethane and other chemicals.

Ethanol, when given orally to mice at doses of 0.125-2.0 g/kg, potentiated both the lethality and behavioral effects (inverted screen test) of inhaled 1,1,1-trichloroethane at concentrations ranging from ≈200 to 10,000 ppm (Woolverton and Balster 1981). In another study, a 3-day pretreatment of mice with ethanol enhanced 1,1,1-trichloroethane-induced liver toxicity, as indicated by an assay of liver function (bromosulfophthalein retention in plasma), but not an assay of liver damage (SGPT levels) (Klaassen and Plaa 1966). Other studies, using only serum enzyme levels to assay liver damage (SGPT or SGOT), found that ethanol markedly and consistently enhanced the hepatotoxicity of more potent chlorinated compounds such as carbon tetrachloride or trichloroethylene, but had no effect on the hepatotoxicity of 1,1,1-trichloroethane (Comish and Adefuin 1966; Klaassen and Plaa 1967). Ethanol may potentiate the hepatotoxicity of chlorinated alkanes because of its ability to induce cytochrome P450IIEl (Ikatsu and Nakajima 1992). The available data indicate that ethanol can enhance the acute neurobehavioral effects of 1,1,1-trichloroethane, but will not cause 1,1,1-trichloroethane to produce severe liver damage (necrosis) like that caused by other chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane.

Co-exposure of control or ethanol-treated rats to inhaled concentrations of 10 ppm carbon tetrachloride and 200 ppm 1,1,1-trichloroethane did not produce changes in several indices of liver damage (SGPT, SGOT, and liver malondialdehyde) compared with exposure to 10 ppm carbon tetrachloride alone (Ikatsu and Nakajima 1992). This indicates that 1,1,1-trichloroethane may be protective against hepatotoxic effects of cytotoxic haloalkanes. In contrast, co-exposure of ethanol-treated rats to 10 ppm carbon tetrachloride and 10-50 ppm chloroform produced liver damage that was greater than the additive effects of exposure to each component alone; this synergistic interaction was not observed in rats fed a diet without ethanol (Ikatsu and Nakajima 1992). Extrapolation of these results to humans suggests that heavy drinkers exposed to mixtures of carbon tetrachloride and chloroform may have a greater risk of developing liver damage than those exposed to either chlorinated alkane alone. The results, however, provide no evidence for a synergistic interaction between carbon tetrachloride and 1,1,1-trichloroethane that would enhance the hepatotoxicity of either compound. In experiments with

isolated rat hepatocytes, concomitant exposure to chloroform, but not co-exposure to 1,1,1-trichloroethane, potentiated carbon tetrachloride-induced lipid peroxidation (Kefalas and Stacey 1991).

Ketones and ketogenic substances (i.e., substances metabolized to ketones or that produce ketosis in the body) potentiate the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane (Plaa 1988). Although the mechanism of this potentiation is not fully understood, Plaa (1988) has proposed enhanced bioactivation of the toxicant through cytochrome P-450 induction. Studies with mice, however, found that treatment with acetone or isopropanol (which is metabolized to acetone) did not enhance the hepatotoxicity of 1,1,1-trichloroethane, but enhanced the threshold doses of chloroform, 1,1,2-trichloroethane, and trichloroethylene to elevate SGPT (Traiger and Plaa 1974). Single intraperitoneal doses of 1,1,1-trichloroethane (1.0 mL/kg) did not produce liver damage (assayed either as elevation in SGPT or in concentrations of liver triglycerides) in control mice or in mice with alloxan-induced diabetes (i.e., that were in a state of ketosis) (Hanasono et al. 1975). Other studies examining the influence of agents that enhance cytochrome P-450 metabolism have provided mixed results. The cytochrome P-450 mixed-function oxidase inducer, phenobarbital, enhanced the hepatotoxicity of 1,1,1-trichloroethane in the rat study by Carlson (1973) but not in that of Cornish et al. (1973). In general, the available data suggest that ketones, ketogenic substances, or cytochrome P-450 inducers will not potentiate 1,1,1-trichloroethane hepatotoxicity.

Concurrent injections of nicotine potentiate the lethality produced by intraperitoneal injection of 1,1,1-trichloroethane in mice (Priestly and Plaa 1976). Although no explanation has been given for the effect of nicotine, stimulation of the sympathetic nervous system and release of epinephrine from the adrenal medulla might enhance cardiac arrhythmias.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,1-trichloroethane than will most persons exposed to the same level of 1,1,1-trichloroethane in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing

compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Limited data from animal studies (Woolverton and Balster 1981) indicate that alcohol drinkers may be more susceptible to the acute neurobehavioral effects of 1,1,1-trichloroethane. Moderate to heavy alcohol drinkers may be more susceptible to the hepatotoxicity of some chlorinated alkanes, such as carbon tetrachloride, chloroform, and 1,1,1-trichloroethane, due to ethanol induction of hepatic cytochrome P-450 isozymes involved in the activation of these compounds to intermediate hepatotoxic metabolites. Available animal studies (Comish and Adefuin 1966; Klaassen and Plaa 1966, 1967), however, have not demonstrated that ethanol ingestion will potentiate the hepatotoxicity of 1,1,1-trichloroethane. Furthermore, evidence indicates that ethanol does not cause 1,1,1-trichloroethane and carbon tetrachloride to interact synergistically to produce hepatotoxic effects, although such an interaction has been demonstrated for ethanol, carbon tetrachloride, and chloroform (Ikatsu and Nakajima 1992). The available data suggest that alcohol ingestion is not likely to significantly potentiate the hepatotoxicity of 1,1,1-trichloroethane.

Diabetics consistently in a state of ketosis may be more susceptible to the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,1-trichloroethane, due to a potentiation from increased ketone levels in the body. Animal studies indicate that the ketone potentiation of the hepatotoxicity of chlorinated alkanes involves an enhancement of the metabolic production of hepatotoxic intermediate metabolites. Available data, however, indicate that ketones do not appreciably potentiate the hepatotoxicity of 1,1,1-trichloroethane (Plaa 1986, 1988). Thus, diabetics in a state of ketosis are not likely to be more susceptible to the hepatotoxicity of 1,1,1-trichloroethane than the population at large.

Because 1,1,1 -trichloroethane is associated with some cardiovascular effects (see Section 2.2.1.2), persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure.

Although no data are available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given period than other people, since most of a single dose is expired (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population.

Young people might be unusually susceptible to 1,1,1-trichloroethane, since the nervous system continues to develop in humans after birth and this chemical may produce residual neurological effects. Developmental toxicity data in humans are not available to address this question. Neurobehavioral testing of exposed rat pups was negative (York et al. 1982). Although limited animal data did not find evidence to support this idea, it remains possible that children might be more susceptible to 1,1,1-trichloroethane than adults.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,1,1-trichloroethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposure to 1,1,1-trichloroethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Ingested 1,1,1-trichloroethane is rapidly absorbed by the gastrointestinal tract of humans and animals (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). To minimize absorption following ingestion, several treatments have been suggested, including administration of milk or water to dilute the gastrointestinal tract contents, gastric lavage, and the administration of emesis-inducing compounds or activated charcoal (Goldfrank et al. 1990; Stutz and Janusz 1988). Butter or some other food high in lipids might be given. The lipids will serve to delay substantially, and possibly diminish, systemic absorption of the 1,1,1-trichloroethane. It should be noted, however, that upon induction of emesis there is the possibility of aspiration of 1,1,1-trichloroethane into the lungs, which may result in pneumonia. Therefore, treatment via stomach pump has been

recommended. Due to rapid absorption of 1,1,1-trichloroethane by the gut, any measures to retard absorption must be taken very rapidly.

Inhaled 1,1,1-trichloroethane is rapidly absorbed and expired, predominantly unchanged, through the lungs (see Section 2.3.). The rapidity with which inhaled 1,1,1-trichloroethane is absorbed (Astrand et al. 1973; Morgan et al. 1972a, 1972b) indicates that assisted ventilation or positive pressure ventilation techniques will not prevent the absorption of 1,1,1-trichloroethane in the lung and emphasizes the importance of removing the subject from the contaminated atmosphere. Nevertheless, such techniques have been suggested to help eliminate the compound from the body (Bronstein and Currance 1988).

The volatility of 1,1,1-trichloroethane is likely to limit absorption of the dermally applied compound, even though dermal absorption under conditions that prevent evaporation is rapid and extensive (Fukabori et al. 1977; Morgan et al. 1991; Stewart and Dodd 1964; Tsuruta 1975). Washing the skin with soapy water has been suggested to reduce the absorption of dermally applied 1,1,1-trichloroethane (Bronstein and Currance 1988; Goldfrank et al. 1990; Stutz and Janusz 1988). Ethyl or isopropyl alcohol also could be used to dilute 1,1,1-trichloroethane on the skin. Flushing the exposed eye with large quantities of water or saline for 15-30 minutes has been suggested to prevent absorption and soothe irritation (Bronstein and Currance 1988; Stutz and Janusz 1988).

2.8.2 Reducing Body Burden

When exposure to 1,1,1-trichloroethane ceases, regardless of route of exposure, the compound is rapidly cleared from the body, predominantly by exhalation of unchanged 1,1,1-trichloroethane in expired air (see Section 2.3.). Very little metabolism of the compound takes place, and despite a preferential distribution of absorbed 1,1,1-trichloroethane to fatty tissues, significant retention does not occur without continued exposure. Thus, continued ventilation by the lungs will eliminate the compound from the body. Suggested methods to assist in lung ventilation include orotracheal and nasotracheal intubation for airway control and positive pressure ventilation techniques (Bronstein and Currance 1988; Ellenhom and Barceloux 1988).

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane are primarily supportive, rather than active, and are not generally directed against a particular mechanism of action (Bronstein and Currance 1988; Ellenhom and Barceloux 1988; Goldfrank et al. 1990; Herd et al. 1974; Stutz and Janusz 1988). Suggested methods of treatment include removing the subject from the source of exposure, ventilation assistance, gastric dilution and lavage for ingested material, oxygen administration, and skin washing. Continuous cardiac monitoring is routine for exposed patients. These methods rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Mechanisms of action, however, are discussed in this section in relation to the possible development of interfering treatment methods.

The mechanism by which 1,1,1-trichloroethane and other organic solvents depress the central nervous system is poorly understood, but is thought to involve interactions of the parent compound with lipids and/o; proteinaceous components of neural membranes (Evans and Balster 1991). No known methods specifically counteract the central nervous system effects of 1,1,1-trichloroethane. Because the specific cellular or biochemical nature of central nervous system depression is poorly understood, it is difficult to propose any method to interfere with this effect of 1,1,1-trichloroethane, other than to prevent further exposure to the compound so that it can be cleared from the body.

The acute cardiotoxic effects of 1,1,1-trichloroethane (reduced blood pressure and increased sensitization to epinephrine-induced arrhythmias) appear to be mediated by the compound and not its metabolites (Carlson 1973; Toraason et al. 1990, 1992) and have been associated with the ability of 1,1,1-trichloroethane to interfere with membrane-mediated processes including calcium mobilization during myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990) and gap junction communication between myocardial cells (Toraason et al. 1992). The administration of epinephrine to counteract 1,1,1-trichloroethane-induced cardiovascular depression has been cautioned against, because of the risk of arrhythmias and ventricular fibrillation (Bronstein and Currance 1988; Goldfrank et al. 1990; Herd et al. 1974). Herd et al. (1974) demonstrated that intravenous injection or infusion of calcium (as calcium gluconate) or phenylephrine protected against 1,1,1-trichloroethane induced blood pressure reduction in anesthetized dogs and suggested more detailed study to assess whether these compounds could be used routinely to resuscitate exposed individuals. Exogenous calcium appears to counteract the influence of 1,1,1-trichloroethane on calcium mobilization during

myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990). Evidence indicates that phenylephrine counteracts 1,1,1-trichloroethane-induced vasodilation without influencing myocardial function (Herd et al. 1974). Further studies examining these active methods of treatment were not located.

Unlike more potent chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane, it is not clear whether the hepatotoxicity of 1,1,1-trichloroethane is due to a metabolite or the parent compound (see Section 2.3.5.). If metabolites produced by cytochrome P-450 oxidation or dechlorination are responsible for the hepatotoxicity, administering cytochrome P-450 inhibitors (e.g., SKF-525A) may inhibit the development of toxic effects on the liver. Clinical or animal studies examining the use of such an approach and the possibility of side effects, however, were not located.

2.9 ADEQUACY OF THE DATABASE

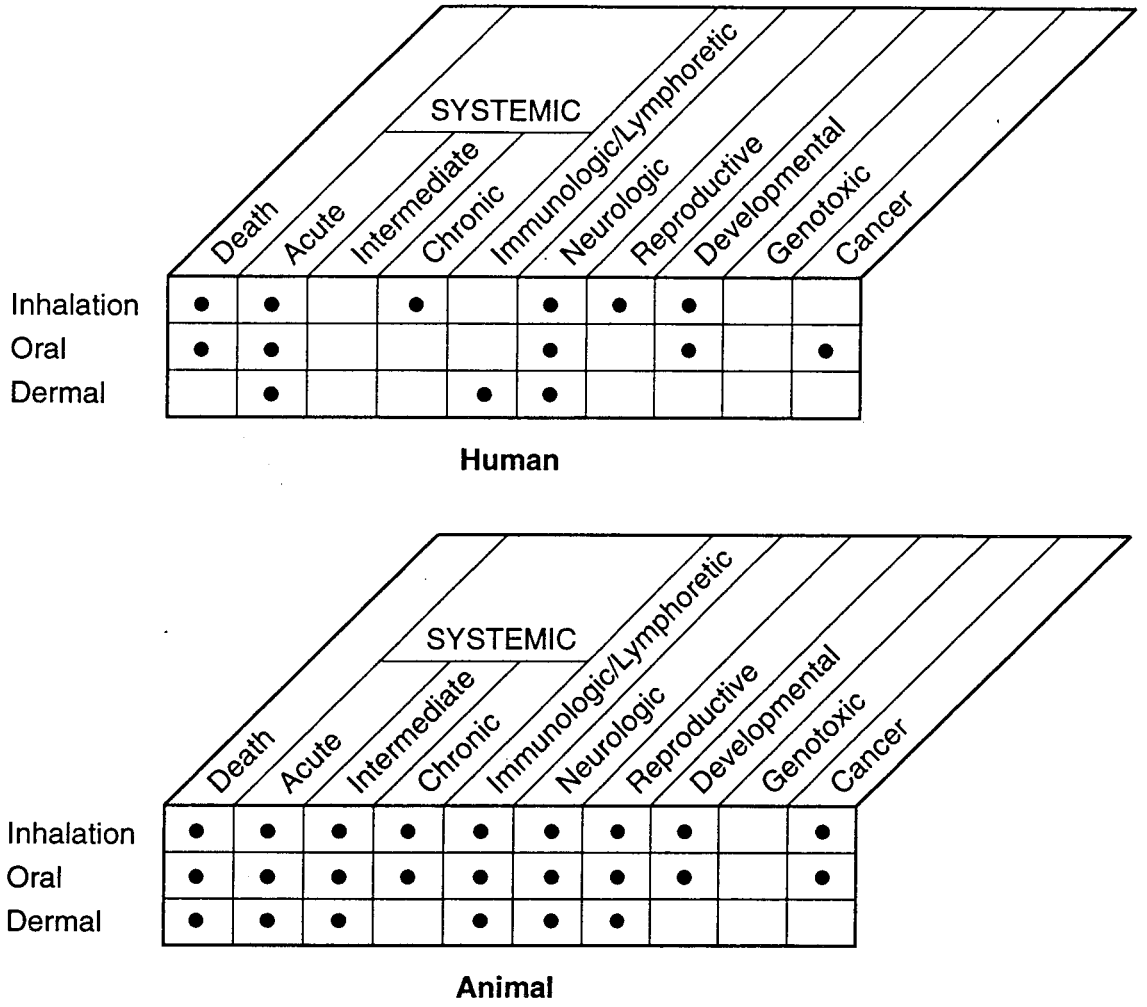
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,1-trichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 1,1,1-Trichloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,1-trichloroethane are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,1-trichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot

FIGURE 2-5. Existing Information on Health Effects of 1,1,1-Trichloroethane



● Existing Studies

does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Several case studies have documented the lethality of high concentrations of inhaled 1,1,1-trichloroethane. Experimental studies, as well as case reports, have reported on acute systemic and neurological effects. Chronic systemic, neurological, developmental, and reproductive effects have been investigated in epidemiology studies. Health effects caused by other routes of administration have not been as well studied in humans. One case study regarding oral exposure to 1,1,1-trichloroethane reported acute systemic effects and investigated potential neurological effects. Developmental effects and cancer from exposure to drinking water were investigated by epidemiology studies. The effects of dermal exposure are discussed in case reports regarding peripheral neuropathy and dermal sensitization in workers and in controlled studies regarding skin irritation.

As indicated in Figure 2-5, many aspects of the health effects resulting from inhalation, ingestion, and dermal exposure to 1,1,1-trichloroethane have been studied in animals. Except for genotoxicity, each of the end points has been investigated in animals exposed to 1,1,1-trichloroethane by the inhalation and oral routes. Fewer end points have been studied following dermal exposure.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. The primary target organs of 1,1,1-trichloroethane toxicity have been identified from human and animal studies. The central nervous system appears to be the most sensitive target organ after inhalation exposure. Decreased psychomotor performance, altered EEG, ataxia, and anesthesia have been observed in humans after inhalation exposure (Domette and Jones 1960; Gamberale and Hultengren 1973; Mackay et al. 1987; Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). Cardiovascular effects (decreased blood pressure and arrhythmias) and mild hepatic effects (increased serum enzyme levels, fatty liver, choles.tasis) have also been observed (Domette and Jones 1960; Guberan et al. 1976; Halevy et al. 1980; Hodgson et al. 1989; Krantz et al. 1959; MacDougall et al. 1987; Stewart 1971; Stewart et al. 1961; Travers 1974). Developmental

toxicity studies in rats and rabbits indicated that 1,1,1-trichloroethane can cause mild developmental delays and effects in the offspring at high levels (usually accompanied by significant maternal toxicity) (BRRC 1987a, 1987b; York et al. 1982). Acute oral studies have determined lethal levels in animals and have shown that ingested 1,1,1-trichloroethane produces neurological effects and reduced body weight gain in animals, and perhaps mild liver effects as well (Bruckner 1983; Spencer et al. 1990; Torkelson et al. 1958; Tyson et al. 1983). The only human data on ingested 1,1,1-trichloroethane was a single case report (Stewart and Andrews 1966). The distribution of 1,1,1-trichloroethane to the central nervous system after oral administration has not been investigated, but is likely to be similar to that following inhalation exposure. In an oral study of rats and mice, however, a significant concentration of 1,1,1-trichloroethane or its metabolites was found in the liver, a possible target organ (RTI 1987). Data from dermal studies indicate only that concentrated 1,1,1-trichloroethane is a skin irritant (Duprat et al. 1976; Stewart and Dodd 1964; Torkelson et al. 1958; Wahlberg 1984a, 1984b). Pharmacokinetic data based on dermal exposures are limited; however, 1,1,1-trichloroethane is absorbed following dermal exposure (Fukabori et al. 1977; Stewart and Dodd 1964; Tsuruta 1975). Therefore, the central nervous system and the liver are likely to be target organs after sufficient dermal exposure, although doses required to produce effects would be difficult to predict. Data from inhalation studies in humans were sufficient to derive an acute inhalation MRL based on decreased psychomotor performance (Mackay et al. 1987). An acute oral MRL, was not derived due to lack of adequate data.

Populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane for brief periods. 1,1,1-Trichloroethane is a frequent contaminant of drinking water supplies, although doses of 1,1,1-trichloroethane ingested by persons living near waste sites are generally significantly lower than doses shown experimentally to cause central nervous system depression or cardiac arrhythmias. Nevertheless, valuable information could be gathered from acute oral toxicity studies with neurological and cardiovascular end points. Similarly, acute dermal studies have focused on death and skin irritation, but have not determined the doses that might produce other effects. This information might be useful because dermal exposure to 1,1,1-trichloroethane is common among workers in certain industries, including those who clean up toxic waste sites.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to 1,1,1-trichloroethane in humans. Data from animal studies indicate that the primary target organs of 1,1,1-trichloroethane after intermediate-duration inhalation exposure are the central nervous

system and the liver. Behavioral effects, decreased activity, and unconsciousness have been reported in animals (Mattsson et al. 1993; Moser et al. 1985; Torkelson et al. 1958), as have chemical changes indicative of physical damage to the brain (Rosengren et al. 1985). Mild hepatic effects such as increased liver weight and fatty changes also have been reported (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Liver necrosis was reported in one study (McNutt et al. 1975). Decreased body weight gain was reported in several studies (Adams et al. 1950; Prendergast et al. 1967). Ingestion studies reported lethality, narcosis, reduced body weight gain, and mild liver effects (Bruckner 1983; NCI 1977). Reproductive and developmental effects also have been investigated following oral exposure (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b). The existing information was considered insufficient for derivation of intermediate-duration oral MRL. Intermediate-duration dermal exposure studies revealed only mild hepatic effects and skin irritation (Torkelson et al. 1958; Viola et al. 1981). Pharmacokinetic data to help identify potential target organs after dermal exposure were not located.

Inhalation data were sufficient to derive an intermediate MRL based on chemical changes suggesting physical damage in the brain of gerbils (Rosengren et al. 1985). Data were not sufficient to derive an intermediate oral MRL. Intermediate-duration oral and dermal exposure studies that attempt to determine NOAEL and LOAEL values for systemic and other neurological effects would be valuable, because populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane by these routes for intermediate periods.

Chronic-Duration Exposure and Cancer. The information provided in the limited number of chronic-duration exposure studies in humans is insufficient to define threshold effect levels. Chronicduration inhalation and oral studies in animals have not defined threshold effect levels for most end points, although LOAEL values were reported for decreased body weight in rats and mice (Maltoni et al. 1986; NCI 1977; Quast et al. 1988). No studies of chronic-duration dermal exposure in humans or animals were located. Pharmacokinetic studies after acute oral exposure indicate that the liver is a potential target organ; the mild liver effects observed in chronic-duration animal studies are supportive (Quast et al. 1988). Existing pharmacokinetic data, however, are not sufficient to identify other target organs after chronic oral, inhalation, or dermal exposure, even though relatively high exposure levels have been tested.

MRL values were not derived for chronic-duration inhalation exposure studies because target organs could not be identified. Similarly, a chronic oral MRL was not derived due to lack of adequate data. Because populations near hazardous waste sites might be chronically exposed to 1,1,1-trichloroethane, studies that attempt to determine threshold effect levels for inhalation, oral, and dermal exposure would be valuable.

Two-year cancer bioassays have been performed following both inhalation and oral exposure. The results of one oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats (Maltoni et al. 1986). Definite conclusions or implications could not be drawn based on this report, however, since experimental procedures were compromised, only one dose level was used and only a small number of rats responded. Although no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988), a followup chronic inhalation bioassay incorporating higher doses, an oral bioassay using several dose levels, larger study groups, and use of more than one species would allow more definitive assessment of 1,1,1-trichloroethane's carcinogenic potential.

Genotoxicity. No studies were located regarding the genotoxic potential of 1,1,1-trichloroethane in humans. Existing genotoxicity studies indicate that 1,1,1-trichloroethane may be weakly mutagenic in *Salmonella* (Gocke et al. 198 1; Nestmann et al. 1980, 1984; Simmon et al. 1977) and is able to transform mammalian cells *in* vitro (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Numerous tests of other genotoxic effects have mostly been negative; however, only a few of these studies made an effort to prevent loss of 1,1,1-trichloroethane due to volatility. Studies designed to account for this property would allow a more complete assessment of genotoxicity. Valuable information also would be provided by tests of chromosomal aberrations in peripheral lymphocytes from humans known to have been exposed to 1,1,1-trichloroethane.

Reproductive Toxicity. An epidemiology study found no relationship between adverse pregnancy outcomes and occupational exposure of fathers to 1,1,1-trichloroethane during spermatogenesis (Taskinen et al. 1989). Limited information regarding reproductive toxicity in animals was located. A multigeneration reproduction study of rats exposed to 1,1,1-trichloroethane in drinking water found no reproductive effects (Lane et al. 1982). Histological evaluation of reproductive organs and tissues after

inhalation exposure of rats and mice revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was observed in guinea pigs (Adams et al. 1950). There are no pharmacokinetic data in humans to help evaluate potential reproductive effects. Reproductive function has not been assessed in animals after inhalation or dermal exposure to 1,1,1-trichloroethane; however, toxicokinetic data available do not suggest route-specific target organs. Nevertheless, an inhalation study of reproductive function in animals would be valuable for assessing reproductive toxicity, since that is the predominant route of exposure for humans to 1,1,1-trichloroethane.

Developmental Toxicity. No relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes (spontaneous abortions/congenital malformations) was found in human epidemiology studies (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Some studies in animals indicate that 1,1,1-trichloroethane is a potential developmental toxicant in quite high doses. Minor skeletal anomalies (delayed ossification and extra ribs in rats and rabbits, respectively, and decreased fetal body weight in rats) have been reported after inhalation exposure of pregnant rats or rabbits during major organogenesis (BRRC 1987a, 1987b; York et al. 1982). These exposures were at concentrations that also produced significant maternal toxicity in two of the studies (BRRC 1987a, 1987b). No neurological effects were reported in the offspring of rats gavaged with 1,1,1-trichloroethane during gestation and lactation (Dow Chemical 1993). A multigeneration developmental study of oral 1,1,1-trichloroethane exposure reported no teratogenic effects in rats (Lane et al. 1982). Although developmental studies by the dermal route are lacking, pharmacokinetic data available do not suggest route-specific target organs. Furthermore, valuable information can be obtained by using the existing physiologically-based pharmacokinetic models once these are validated by comparison with 1,1,1-trichloroethane levels measured over time in different tissues for the different exposure routes.

Immunotoxicity. No studies were located regarding the immunotoxicity of 1,1,1-trichloroethane in humans. Information regarding the lymphoreticular system was limited to reports of spleen congestion in subjects acutely exposed to high levels of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969). Exposed mice were not more susceptible to bacterial infection than unexposed control mice after a single inhalation exposure to 1,1,1-trichloroethane (Aranyi et al. 1986). Very limited information exists regarding histology and function of tissues of the lymphoreticular system after

1,1,1 -trichloroethane exposure by any route. Histological evaluation of lymphoreticular tissues, including lymph nodes, thymus, and spleen, revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Tdrkelson et al. 1958).

An acute- or intermediate-duration exposure study including a comprehensive evaluation of lymphoid tissues and blood components would provide valuable information regarding potential immunotoxicity.

Neurotoxicity. The central nervous system is apparently the primary target organ of 1,1,1-trichloroethane toxicity. Behavioral effects, altered EEG recordings, ataxia, unconsciousness, and death have been reported in human and animal studies (Albee et al. 1990a, 1990b; Clark and Tinston 1982; DeCeaurriz et al. 1983; Dornette and Jones 1960; Evans and Belster 1993; Gamberale and Hultengren 1973; Gehring 1968; Kelafant et al. 1994; Mackay et al. 1987; Mattsson et al. 1993; Moser and Balster 1985, 1986; Spencer et al. 1990; Stewart et al. 1961, 1969; Torkelson et al. 1958). Neurochemical changes following prolonged inhalation exposure, suggesting morphological damage to the brain, have been reported in gerbils (Rosengren et al. 1985). Respiratory depression appears to cause death in humans and animals. Most studies were conducted by inhalation exposure, but limited data on oral exposure were also available, including a recent study in which no neurological effects were reported in the offspring of rats treated during gestation and lactation (Dow Chemical 1993) (see Developmental Effects). Neurological effects have not been reported after dermal exposure.

Additional in-depth studies of the effects of 1,1,1-trichloroethane on neurological structure and function might provide important information regarding the mechanisms and reversibility of 1,1,1-trichloroethane-induced neurological dysfunction. Studies to follow-up on the reported changes in GFA protein following 1,1,1-trichloroethane exposure may be helpful. Acute-, intermediate-, and chronic-duration exposure studies by the oral route, including comprehensive histological evaluations and nervous system function tests, would provide information regarding the dose-response relationship for this route of exposure. An acute-duration dermal exposure to assess the potential for neurotoxicity by this route would also be useful, although toxicokinetic data available do not suggest route-specific target organs. Populations residing near hazardous waste sites or in occupational settings might be exposed to 1,1,1-trichloroethane. Well-designed and controlled epidemiology studies of these populations may provide useful information on the potential for 1,1,1-trichloroethane at relevant exposure levels to produce neurological disturbances in humans.

Epidemiological and Human Dosimetry Studies. Epidemiology studies have investigated the relationship between long-term exposure to 1,1,1-trichloroethane and systemic, neurological, reproductive, developmental, and cancer effects in humans, but no health effects associated with exposure have been reported. These studies, however, are limited in design and scope and do not provide definitive conclusions regarding the health effects of 1,1,1-trichloroethane exposure. More extensive studies might provide a definitive assessment of the health hazards of chronic 1,1,1-trichloroethane exposure in humans, especially for occupationally exposed populations. If such effects are identified, human dosimetry studies may be able to correlate 1,1,1-trichloroethane levels in human tissues or fluids with chronic health effects. The usefulness of such studies on individuals living near hazardous waste sites is questionable since exposure is relatively low and the half-life of 1,1,1-trichloroethane and its metabolites too short. Acute experimental studies in humans have established inhalation exposure levels associated with acute neurological effects. Subpopulations potentially exposed to 1,1,1-trichloroethane include people residing near hazardous waste sites where the chemical is stored, people who encounter it in the workplace (either in its manufacture or application), and people who use household products that contain it. It should be mentioned, however, that as a result of Title VI of the Clean Air Act, potential human exposure to 1,1,1-trichloroethane is expected to be gradually reduced (see Chapter 5).

Biomarkers of Exposure and Effect

Exposure. Known biomarkers of 1,1,1-trichloroethane exposure include blood, breath, and urine levels of the chemical and its two major metabolites, trichloroethanol and trichloroacetic acid. Metabolism of trichloroethylene and perchloroethylene also produces trichloroethanol and trichloroacetic acid; therefore, these metabolites are not unique to 1,1,1-trichloroethane (Monster 1988). Environmental 1,1,1-trichloroethane levels are significantly correlated with the levels in blood, breath, and urine (Hartwell et al. 1987a; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987~). 1,1,1-Trichloroethane is rapidly cleared from the body after exposure (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). The two metabolites have a much longer half-life in the body than the parent compound. Therefore, 1,1,1-trichloroethane levels in the blood, breath, and urine may be used as biomarkers only if they are measured during or shortly after exposure. The two metabolites are more useful as biomarkers for a somewhat longer period after exposure. Because 1,1,1-trichloroethane's half-life in the body is short, and because hematological profiles and clinical

chemistry parameters are not usually affected, the further development of biomarkers based on easilyobtained biological fluids may not be useful.

Effect. No specific biomarkers of effect for 1,1,1-trichloroethane were located in the literature. The central nervous system is apparently the most sensitive organ in humans and animals, and neurotoxicity (decreased psychomotor performance, ataxia, and unconsciousness) is observed after short-term high-level exposure. Development of specific biomarkers of effect would facilitate medical surveillance, which could lead to early detection of adverse effects.

Absorption, Distribution, Metabolism, and Excretion. The absorption, metabolism, and elimination of 1,1,1-trichlorokthane have been studied extensively in humans and animals. Distribution has not been as well studied. 1,1,1-Trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals (Astrand et al. 1973; Fukabori et al. 1977; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966; Stewart and Dodd 1964; Tsuruta 1975). As duration of inhalation exposure increases in humans and animals, the percentage net absorption decreases, because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. A study with humans equipped with respirators indicated that, during exposure to 1,1,1-trichloroethane vapors in the atmosphere, absorbed doses from inhaled 1,1,1-trichloroethane are much larger than doses from dermal absorption (Riihimaki and Pfaffli 1978). Animal studies demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including developing fetuses, with preferential distribution to fatty tissues (Holmberg et al. 1977; Schumann et al. 1982a; Takahara 1986b). Human data regarding the compound's distribution are limited to the observation that detectable levels were found in subcutaneous fat, kidney fat, liver, lung, and muscle in 30 autopsy cases (Alles et al. 1988). The predominant pathway of 1,1,1-trichloroethane elimination by humans and animals, regardless of exposure route, is exhalation of the unchanged compound (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Schumann et al. 1982a, 1982b). When exposure ceases, the compound rapidly clears from the body. Only trace amounts of the compound remained in animal tissues within days of short-term exposure. Further studies in humans regarding extent and rates of absorption and elimination with dermal exposure to aqueous 1,1,1-trichloroethane solutions or suspensions under conditions allowing evaporation from the skin may provide useful information on dermal contact with contaminated water.

Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the exposure route (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Schumann et al. 1982a, 1982b). 1,1,1-Trichloroethane is metabolized oxidatively to trichloroethanol and trichloroacetic acid by a concentration-dependent, saturable process that appears to involve the cytochrome P-450 mixed-function oxidase system. These metabolites have been detected in urine excreted from exposed humans and animals; other minor metabolites (CO_2 and acetylene, the latter formed by the reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply) are eliminated in expired air.

The hepatotoxicity of 1,1,1-trichloroethane is quite low compared to other chlorinated hydrocarbons, including 1,1,1-trichloroethane. The relatively low toxicity of 1,1,1-trichloroethane may be due to its relatively low metabolism rate, since the more hepatotoxic halocarbons are extensively metabolized. Whether the mild effects of repeated 1,1,1-trichloroethane exposure are evoked by the parent compound or the limited quantities of metabolites produced is not known, however. The available data indicate that the acute effects on the central nervous and the cardiovascular systems are caused by 1,1,1-trichloroethane and not its metabohtes. The interference of 1,1,1-trichloroethane with membrane mediated processes, due to lipophilicity, may be responsible for the acute effects on these systems; several cellular and biochemical processes appear to be affected by 1,1,1-trichloroethane.

Comparative Toxicokinetics. The toxicokinetic pattern of 1,1,1-trichloroethane is qualitatively similar in humans, rats, and mice. There are major quantitative differences, however, including a higher blood:air partition coefficient, higher respiratory and circulatory rates, and increased rate of metabolism in mice. This comparison has led to a suggestion that rats may be a better model for humans than mice. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Leung 1992; Nolan et al. 1984; Reitz et al. 1988; USAF 1990). Further research verifying the metabolic constants and other input parameters (partition coefficients, tissue values and blood flows, cardiac output, and respiratory volumes) used in these models might improve the accuracy and utility of the models in interspecies extrapolations.

Methods for Reducing Toxic Effects. Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane and other halogenated hydrocarbons are generally supportive and rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Animal studies indicate that intravenous injection or infusion of calcium gluconate or phenylephrine are protective against acute blood pressure reduction caused by exposure to 1,1,1-trichloroethane (Herd et al. 1974). Further animal testing is needed to assess whether these compounds might be used to resuscitate individuals exposed to high concentrations of 1,1,1-trichloroethane.

2.9.3 Ongoing Studies

J.L. Poyer of the Oklahoma Medical Research Foundation is examining the correlation between hepatic free radical formation (determined with electron spin resonance techniques) and liver injury (assessed by electron microscopy and serum sorbitol dehydrogenase) in rats treated with a series of halogenated hydrocarbons including 1,1,1-trichloroethane (CRISP 1992). Investigations will include determining the capacities of free radical quenching and trapping agents to prevent liver injury.

A. Braun is conducting a 13-week dietary study of 1,1,1-trichloroethane in rats and mice (CRISP Database 1992). The study will include hematological and clinical chemistry examinations, sperm morphology and vaginal cytology examinations, and urinary metabolite analysis.

Dr. R. Balster and his colleagues at the Medical College of Virginia will examine the effects of 1,1,1-trichloroethane in mice relative to those of ethanol and other drugs of abuse (FEDRIP 1994). Dr. Balster proposes to develop new behavioral test procedures to study inhalant-self administration, place preference conditioning, effects on motor activity, multiple-schedule performance; and punished responding.

Dr. J. Bruckner and his colleagues at the University of Georgia are collaborating with EPA scientists to develop more accurate PBPK models for prediction of time integrals of target organ exposure to 1,1,1-trichloroethane.

3. CHEMICAL AND PHYSICAL INFORMATION

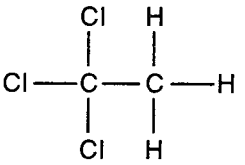
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 1,1,1-trichloroethane is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 1 ,l ,I -trichloroethane is located in Table 3-2.

TABLE 3-1. Chemical Identity of 1,1,1-Trichloroethane

Characteristic	Information	Reference
Chemical name	1,1,1-Trichloroethane	CAS 1994
Synonym(s)	Methylchloroform	CAS 1994
	Methyltrichloromethane	SANSS 1994
	Trichloromethylmethane	
	α-Trichloromethane	
Registered trade name(s)	Chlorothene NU	OHM-TADS 1994
	Aerothene TT	
Chemical formula	CCl_3CH_3	CAS 1994
Chemical structure		
Identification numbers:		
CAS registry	71-55-6	CAS 1994
NIOSH RTECS	KJ2975000	RTECS 1994
EPA hazardous waste	U226	HSDB 1994
OHM/TADS	8100101	OHM/TADS 1994
DOT/UN/NA/IMCO shipping	UN 2831	HSDB 1994
HSDB	157	HSDB 1994
NCI	C04626	HSDB 1994

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of 1,1,1-Trichloroethane

Property	Information	Reference
Molecular weight	133.4	CAS 1993
Color	Colorless	Archer 1979; Sax and Lewis 1987
Physical state	Liquid	Merck 1989
Melting point	–30.4 °C –33.0 °C	Weast 1988 Archer 1979
Boiling point	74.1 °C	Merck 1989
Density:		
at 20 °C	1.3390 g/mL	Weast 1988
at 25 °C	1.3299 g/mL	Riddick et al. 1986
at 30 °C	1.32096 g/mL	Riddick et al. 1986
Odor	Ethereal, chloroform-like	Archer 1979; Aviado et al. 1976
Odor threshold:		
Water	No data	
Air	120 ppm 500 ppm	Amoore and Hautala 1983; Reist and Rex 1977
Solubility:		
Water at 20 °C	0.1495% (wt/wt)	Horvath 1982
Organic solvent(s)	Soluble in alcohol, ether, chloroform; miscible with other chlorinated solvents; soluble in common organic solvents	Weast 1988; Archer 1979
Partition coefficients:		
Log K_{ow}	2.49	Hansch and Leo 1985
Log K_{oc}	2.03	Friesel et al. 1984
	2.02	Chiou et al. 1979
Vapor pressure at 20 °C	124 mm Hg 16.4 1kPa	Boublik et al. 1984 Riddick et al. 1986
Henry's law constant:		
at 20 °C	6.3×10^{-3} atm-m^3/mol	Chiou et al. 1980
at 30 °C	17.2×10^{-3} atm-m^3/mol	Gossett 1987
Autoignition temperature	537 °C	HSDB 1992
Flashpoint	None	Archer 1979
Flammability limits	8–10.5%	Archer 1979
Conversion factors		
ppm (v/v) to mg/m^3 in air (20 °C)	1 ppm = 5.4 mg/m^3	Chiou et al. 1980
mg/m^3 to ppm (v/v) in air (20 °C)	1 mg/m^3 = 0.185 ppm	
Explosive limits	7.5–12.5% in air	NIOSH 1990

CAS = Chemical Abstracts Services; HSDB = Hazardous Substances Data Bank; NIOSH = National Institute for Occupational Safety and Health; v/v = volume by volume; wt/wt = weight by weight

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

According to the United States International Trade Commission publication on U.S. production and sales of synthetic organic chemicals (USITC 1991), 802.6 million pounds of 1,1,1-trichloroethane were produced in 1990. Three chemical companies are listed as domestic manufacturers in 1994: Dow Chemical in Freeport, Texas; Vulcan Materials Co. Chemicals Division in Geismer, Louisiana; and PPG Industries in Lakes Charles, Louisiana (SRI 1994). The estimated total production capacity at each of the facilities in 1994 (in millions of pounds) is 500 for Dow's plant in Freeport, Texas; 350 for PPG's plant in Lake Charles, Louisiana; and 200 for Vulcan's plant in Geismar, Louisiana (estimated total capacity of 1,050 million pounds as of January 1, 1994) (SRI 1994). The estimated total capacity at these facilities was 1,062 million pounds as of January 1, 1991 (SRI 1991). U.S. production in 1990 was ≈76% of capacity. The total production volume of 1,1,1-trichloroethane in previous years by the same manufacturers was 723.7 and 783.1 million pounds in 1988 and 1989, respectively (USITC 1989, 1990). The demand for 1,1,1-trichloroethane exhibited a 0.8% growth per year from 1982 to 1991. Future growth has been projected to decline 11.6% per year through 1996 (Chemical Marketing Reporter 1992). According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, U.S. production of 1,1,1-trichloroethane will be cut incrementally until the proposed phase-out occurs by January 1996 (EPA 19931). Despite the mandated cuts in production, supplies of 1,1 ,l-trichloroethane should remain available over the next 5 years due to decreased demand as a result of availability of substitutes (Chemical Marketing Reporter 1992).

Besides the above producers of 1,1,1-trichloroethane, Table 4-l reports the number of facilities in each state that manufacture and process 1,1,1-trichloroethane, the intended use of the product, and the range of maximum amounts of 1,1,1-trichloroethane stored on site. The data reported in Table 4-1 are derived from the Toxics Release Inventory (TRI) (TR192 1994). Only certain types of facilities were required to report to the TRI databank of EPA. Hence, this is not an exhaustive list.

The most common method for industrial preparation of 1,1,1-trichloroethane is the reaction of hydrochloric acid with vinyl chloride (obtained from 1,2-dichloroethane) to obtain 1,1-dichloroethane, followed by either thermal or photochemical chlorination. Other methods include the catalyzed addition of hydrogen chloride to 1,1-dichloroethylene, and the direct chlorination of ethane itself,

Table 4.1 Facilities That Manufcture or Process 1,1,1-Trichloroethane

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds [b]	Activities and uses[c]
AL	41	0-100	1, 2, 3, 8, 10, 11, 12, 13
AR	43	0-100	8, 11, 12, 13
AZ	42	0-1000	2, 3, 7, 8, 9, 11, 12, 13
CA	470	0-50000	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
CO	22	0-100	2, 8, 9, 11, 12, 13
CT	109	0-1000	2, 3, 6, 8, 9, 10, 11, 12, 13
DE	1	1-10	2, 3, 8, 10, 12
FL	65	0-100	1, 2, 3, 8, 9, 10, 11, 12, 13
GA	84	0-1000	2, 3, 4, 8, 9, 10, 11, 12, 13
IA	41	0-1000	8, 10, 11, 12, 13
ID	2	1-10	12, 13
IL	167	0-50000	1, 2, 4, 7, 8, 9, 10, 11, 12, 13
IN	134	0-1000	1, 2, 3, 8, 9, 10, 11, 12, 13
KS	27	0-1000	2, 3, 8, 9, 10, 11, 12, 13
KY	43	0-10000	2, 7, 8, 10, 12, 13
LA	22	0-50000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,
MA	92	0-1000	2, 3, 8, 9, 10, 11, 12, 13
MD	28	1-1000	8, 10, 11, 12, 13
ME	17	0-100	11, 12, 13
MI	106	0-10000	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13
MN	70	0-1000	2, 3, 7, 8, 9, 10, 11, 12, 13
MO	72	0-500000	2, 3, 8, 9, 10, 11, 12, 13
MS	37	0-1000	2, 3, 4, 8, 9, 10, 11, 12, 13
NC	133	0-1000	2, 3, 8, 9, 10, 11, 12, 13
ND	4	1-100	11, 13
NE	24	1-100	8, 11, 12, 13
NH	27	0-100	8, 10, 12, 13
NJ	86	0-10000	2, 3, 7, 8, 10, 12, 13
NM	6	0-100	8, 9, 12, 13
NV	2	0-100	13
NY	127	0-1000	1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13
OH	226	0-50000	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
OK	29	0-100	8, 10, 11, 12, 13
OR	17	0-100	8, 11, 12, 13
PA	145	0-1000	2, 3, 8, 9, 10, 11, 12, 13
PR	16	0-100	8, 9, 13
RI	38	0-100	2, 3, 8, 11, 12, 13
SC	52	0-10000	2, 3, 8, 9, 10, 11, 12, 13
SD	8	0-100	11, 12, 13
TN	77	0-1000	2, 3, 5, 8, 10, 11, 12, 13

Table 4.1 Facilities That Manufcture or Process 1,1,1-Trichloroethane (continued)

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds [b]	Activities and uses[c]
TX	150	0-10000	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
UT	20	0-1000	8, 9, 12, 13
VA	47	0-100	7, 8, 11, 12, 13
VI	1	10-100	7
VT	15	1-100	11, 12, 13
WA	30	0-1000	1, 2, 3, 5, 8, 11, 12, 13
WI	111	0-1000	7, 8, 10, 11, 12, 13
WV	5	1-100	10, 12, 13

Source: TRI92 1994

[a]Post office state abbreviations used
[b]Data in TRI are maximum amounts on site at each facility.
[c]Activities/Uses

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a byproduct
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

followed by separation from the other products produced (Archer 1979). Commercial grades of 1, 1 , 1 -trichloroethane usually contain some inhibitor, such as nitromethane, methyl ethyl ketone, toluene, 1,6-dioxane, butylene oxide, 1,3-dioxolane, or secondary butyl alcohols (Archer 1979; OHM/TADS 1992).

4.2 IMPORT/EXPORT

According to the Commerce Department's National Trade Data Bank (NTDB 1994), the following amounts of 1,1,1-trichloroethane (in pounds with kg in parentheses) were exported from the United States during the period 1989-1993: 124.3 million (56.4 million) in 1989; 114.6 million (52.0 million) in 1990; 162.4 million (73.7 million) in 1991; 139.7 million (63.4 million) in 1992; and 75.8 million (34.4 million) in 1993. The amount of 1,1,1-trichloroethane exported has declined since 1991. Because 1,1,1-trichloroethane may be an ozone-destroying chemical, its export and import will sharply decline in future years as a result of the Montreal Protocol. The following amounts of 1,1,1-trichloroethane (in pounds with kg in parentheses) were imported into the United States: 0.1 million (0.05 million) in 1991; 13.2 million (6.0 million) in 1992; and 0.2 million (0.1 million) in 1993 (NTDB 1994).

4.3 USE

1,1,1-Trichloroethane was developed initially as a safer solvent to replace other chlorinated and flammable solvents. Current uses of 1,1,1-trichloroethaue and percentages of total amount devoted to each use are: vapor degreasing, 31%; cold cleaning, 18%; aerosols, 12%; adhesives, 10%; chemical intermediate, 10%; coatings and inks, 7%; textiles, 4%; electronics, 3%; other, 5% (Chemical Marketing Reporter 1992).

1,1,1-Trichloroethane is used as a solvent for adhesives (including food packaging adhesives) and in metal degreasing, pesticides, textile processing, cutting fluids, aerosols, lubricants, cutting oil formulations, drain cleaners, shoe polishes, spot cleaners, printing inks, and stain repellents, among other uses. It is used in industry primarily for cold-cleaning, dip cleaning, bucket cleaning, and vapor degreasing operations of items such as precision instruments, molds, electrical equipment, motors, electronic components and instruments, missile hardware, paint masks, photographic film, printed circuit boards, generators, switchgears, semiconductors, high vacuum equipment, fabrics, and wigs. It is also used for on-site cleaning of printing presses, food packaging machinery, and molds.

1,1,1-Trichloroethane is also used as a chemical intermediate in the production of vinylidene chloride. It was formerly used as a food and grain fumigant (Archer 1979; Aviado et al. 1976, 1980; Merck 1989; Sax and Lewis 1987; Stewart 1983; WHO 1992).

1,1,1-Trichloroethane is used extensively in household products. In a recent "shopping basket" survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products chosen as likely to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in 32 of 67 categories (1,026 brands sampled) of common household products at concentrations >l% by weight; trace amounts were listed in all 67 categories (Frankenberry et al. 1987; Maklan et al. 1987). Some of the several commonly used household items that may contain 1,1,1-trichloroethane are shown in Table 4-2. 1,1,1-Trichloroethane is emitted during use of items prevalent in the average home (Pleil and Whiton 1990; Wallace et al. 1987b).

4.4 DISPOSAL

1,1,1-Trichloroethane has been identified as a hazardous waste by EPA, and disposal of this waste is regulated under the Federal Resource Conservation and Recovery Act (RCRA). Specific information regarding federal regulations on 1,1,1-trichloroethane disposal on land, in municipal solid waste landfills, in incinerators, and during underground injection is available in the Code of Federal Regulations (EPA 1992a, 1992b, 1992c, 1992d). Disposal of 1,1,1-trichloroethane can be accomplished through its destruction in a high temperature incinerator equipped with a hydrochloric acid scrubber. The destruction and removal efficiency (DRE) for 1,1,1-trichloroethane in hazardous wastes must attain 99.99% (Carroll et al. 1992). Potential methods of incineration include liquid injection, rotary kiln, and fluidized bed incineration (Carroll et al. 1992; HSDB 1994). Product residues and sorbent media may be packaged in a 17H epoxy-lined drum, encapsulated in an organic polyester resin, and disposed of at an approved EPA disposal site (OHM/TADS 1992). Other methods that have shown promise for the destruction of 1,1,1-trichloroethane are homogeneous sonochemical treatment for aqueous wastes (Cheung et al. 1991) and a combination of ozonation and ultraviolet treatment for groundwater (Kusakabe et al. 1991). From a laboratory feasibility study, it was concluded that the in situ biodegradation of 1,1,1-trichloroethane in soils by methane-oxidizing bacteria was not a viable bioremediation method (Broholm et al. 1991).

TABLE 4-2. 1,1,1-Trichloroethane in Common Household Products[a]

Product	Concentration (% w/w)[b]
Adhesive cleaners	0.1–95.0
Adhesives	0.2–121.1
Aerosol spray paint	0.2–1.0
Battery terminal protectors	37.1
Belt lubricants	11.4–72
Brake cleaners	0.4–75.6
Carburetor cleaners	0.2–0.3
Circuit board cleaners	NS
Door spray lubricants	95.6
Drain cleaner (nonacid)	97.8
Electric shaver cleaners	2.5–20.3
Engine degreasers	0.2
Fabric finishes	77.9–85.1
Gasket removers/adhesives	0.2–1.0
General purpose spray degreasers	0.1–71.4
General purpose liquid cleaners	72.7–126.7
Ignition wire driers	24.3–43.6
Lubricants	0.1–104.5
Miscellaneous nonautomotive	12.5–67.5
Miscellaneous automotive	0.3–0.4
Oven cleaners	97
Paint removers/strippers	0.1–25.7
Primers	1.2–61.8
Rust removers	0.7
Silicone lubricants	0.2–91.1
Specialized aerosol cleaners	0.2–83.8
Spot removers	10.5–110.8
Spray shoe polish	11.4–62.3
Stereo/record player cleaners	0.7
Suede protectors	4.8–118.5
Tape recorder cleaners	0.2–101.5
Tire cleaners	0.1–90.3
Transmission cleaner/lubricant	113
TV/computer screen cleaners	0.3
Typewriter correction fluid	6–110
VCR cleaners	97.8
Video disk cleaners	0.6
Water repellents	0.2–116.2
Wood cleaners	12.3–20.4
Woodstain/varnishes/finishes	0.1–21.4

[a]Source: Adapted from Frankenberry et al. 1987; Maklan et al. 1987
[b]Average recovery from spiked samples: 97±13%

w/w = weight per weight

5. POTENTIAL FOR HUMAN EXPOSURE

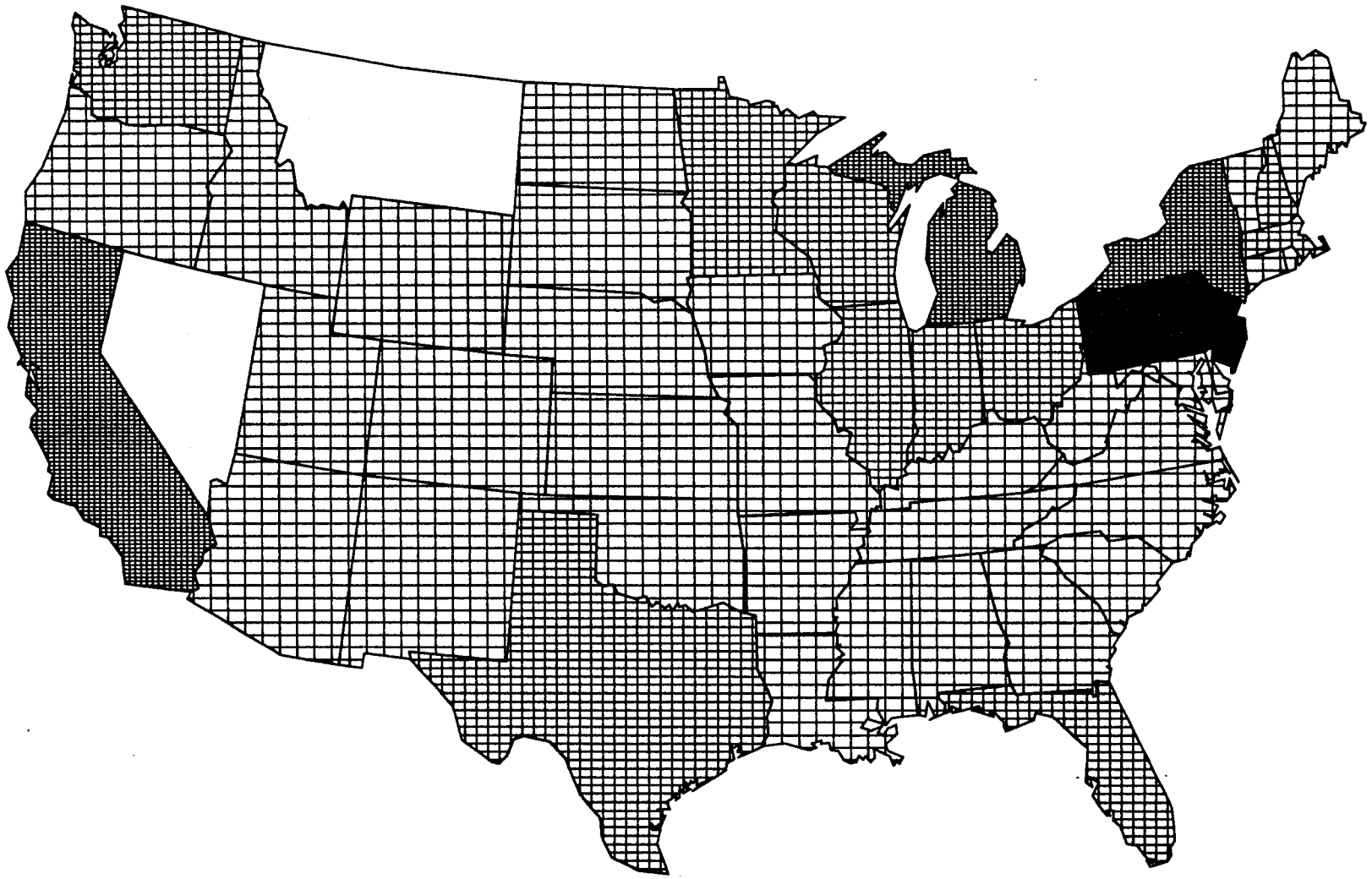
5.1 OVERVIEW

1,1,1-Trichloroethane is a synthetic compound that is released to the environment by human industrial activity. It may be released to the environment by process and fugitive emissions during its manufacture, formulation, and use in both consumer and industrial products. Because 1,1,1-trichloroethane is volatile and is used as a solvent in many products, it is most frequently found in the atmosphere due to volatilization during production and use.

Exposure to 1,1,1-trichloroethane can occur by inhalation, dermal contact, or through the ingestion of either contaminated water or food. Exposure by inhalation is expected to predominate. The general population can be exposed to 1,1,1-trichloroethane because of its prevalence in common household products. Indoor air concentrations have been determined to be greater than nearby outdoor concentrations, probably as a result of its presence in a myriad of consumer products. Occupational exposure to 1,1,1-trichloroethane can occur by inhalation or dermal contact during its manufacture and formulation, during its use as a cleaner of manufactured components, and during the application of the numerous paints, resins, adhesives, and cleaners containing it as a solvent. At hazardous waste sites, inhalation is expected to be the predominant route of exposure; however, ingestion of contaminated water may occur also. 1,1,1-Trichloroethane has been identified in 696 of the 1,408 NPL hazardous waste sites (HazDat 1994). The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 694 are located in the United States and 2 are located in the Commonwealth of Puerto Rico (not shown in Figure 5-l).

The dominant environmental fate process for 1,1,1-trichloroethane is volatilization to the atmosphere. Once in the atmosphere, reaction with photochemically-produced hydroxyl radicals is expected to be the most important transformation process for 1,1,1-trichloroethane; the estimated atmospheric lifetime for this process is about 6 years. This long atmospheric lifetime allows about 15% of 1,1,1-trichloroethane to migrate to the stratosphere, where it may be degraded by lower wavelength ultraviolet light, not available in the troposphere, to produce atomic chlorine. The chlorine atoms produced in the stratosphere by this process may react with ozone causing the erosion of the ozone layer. However, direct photochemical degradation of 1,1,1-trichloroethane in the troposphere should not occur. The moderate water solubility of 1,1,1-trichloroethane suggests that rain washout can occur; however,

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 1,1,1-TRICHLOROETHANE CONTAMINATION *



*Derived from HazDat 1994

1,1,1-trichloroethane removed from the atmosphere by this process would be expected to re-volatilize. The lengthy half-life for 1,1,1-trichioroethane in the troposphere allows it to be carried great distances from its original point of release, and it has been found in remote places far from any known source of release.

If released to soil, 1,1,1-trichloroethane should display high mobility and the potential for leaching into groundwater. Volatilization from soil surfaces to the atmosphere is expected to be an important fate process. Although data regarding biodegradation of 1,1,1-trichloroethane in soil are lacking, it is not expected to be an important fate process. 1,1,1-Trichloroethane is not expected to undergo aerobic biodegradation, but there is some experimental evidence that biodegradation may occur under anaerobic conditions.

Once released to surface water, 1,1,1-trichloraethane is expected to undergo volatilization to the atmosphere. Neither adsorption to sediment nor bioconcentration in aquatic organisms is recognized as an important removal process. Aerobic biodegradation of 1,1,1-trichloroethane can occur in the presence of methane-oxidizing bacteria. If released to groundwater, biodegradation of 1,1,1-trichloroethane under anaerobic conditions is known to occur; however, it appears to be a slow process under most environmental conditions.

1,1,1-Trichloroethane may very slowly undergo abiotic degradation in soil or water by elimination of hydrochloric acid (HCl) to form 1,1-dichloroethene, which also can be considered a pollutant, or it can undergo hydrolysis to form the naturally occurring acetic acid. Direct photochemical degradation is not expected to be an important fate process.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

A correlation of data from the EPA Air Toxics Emission Inventory with industrial source codes (SIC codes), shows that volatile emissions of 1,1,1-trichloroethane are associated with 122 different industrial classifications that run the gamut from manufacturing and formulation to secondary uses (Pacific Environmental Services, Inc. 1987). Release of 1,1,1-trichloroethane in most cases is an expected result of its use (Spence and Hanst 1978). Small amounts of 1,1,1-trichloroethane are also

released to the atmosphere from coal-fired power plants (Garcia et al. 1992), from incineration of hospital wastes (Green et al. 1992; Walker and Cooper 1992), incineration of military nerve agents (Mart and Henke 1992), incineration of industrial wastes containing certain plastics and waste solvents (Nishikawa et al. 1992, 1993), and incineration of municipal waste water sludge (Vancil et al. 1991). 1,1,1-Trichloroethane contained in consumer products is released into the atmosphere during the application, drying, or curing of these products. 1,1,1-Trichloroethane can enter the atmosphere via the air-stripping treatment of waste water. Volatilization, which accounts for ≈100% of removal in waste water, occurs during this process (Kincannon et al. 1983a). Volatilization from waste lagoons is also likely (Shen 1982).

Precise quantitative data on 1,1,1-trichloroethane air emissions are lacking. A large proportion of total production probably finds its way into the atmosphere. Estimates for 1984 suggest that 100.4 kilotons (220 million pounds) were released during use by the European Economic Community (EEC) and other western European countries, a figure representing some 70% of total consumption in Europe (Herbert et al. 1986). Recent global estimates indicate that 1,497 million pounds (679 million kg) of 1,1,1-trichloroethane were released to the atmosphere in 1988 (Midgley 1989). 1,1,1-Trichloroethane releases in air from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 1992 are reported in the Toxics Release Inventory and listed in Table 5- 1 (TR192 1994). According to TR192 (1994), an estimated total of ≈115 million pounds of 1,1,1-trichloroethane, amounting to ≈99.9% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1992. The TRI data should be used with caution since only certain types of facilities were required to report. This is not an exhaustive list. However, a comparison of TRI data for 1990 and 1992 (163 million pounds and 115 million pounds, respectively) shows that the nationwide emission of 1,1,1-trichloroethane in the atmosphere has decreased by ≈29% during this period. A 36% reduction in atmospheric emissions was observed in Irvine, California, from 1990 to 1989 (Brown and Hart 1992). Most processes that use 1,1,1-trichloroethane result in some fugitive emissions. For example, the release of 1,1,1-trichloroethane from an industrial solvent recycling facility was 16.7% of the throughput (Balfour et al. 1985).

5.2.2 Water

1,1,1-Trichloroethane can be released to surface water from the waste water of industries in any of the numerous industrial classifications that use or produce this compound. The STORET database for

Table 5.1 Releases to the Environment from Facilities That Manufcture or Process 1,1,1-Trichloroethane

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground Injection	Total Environment[c]	POTW Transfer	Off-site Waste Transfer
AL	41	250-300000	0-750	0-0	0-0	250-300005	0-5	0-450320
AR	43	684-213785	0-5	0-0	0-0	684-213785	0-5	0-143772
AZ	42	250-380000	0-0	0-0	0-0	250-380000	0-5	0-82354
CA	470	0-1108915	0-81	0-14394	0-0	0-1108915	0-18759	0-166826
CO	22	0-160000	0-0	0-0	0-0	0-160000	0-5	0-13200
CT	109	0-762600	0-50	0-0	0-0	0-762600	0-250	0-375675
DE	1	1200-1200	0-0	0-0	0-0	1200-1200	0-0	0-0
FL	65	0-221578	0-0	0-0	0-3	0-221578	0-250	0-32065
GA	84	0-714095	0-1	0-0	0-0	0-714095	0-250	0-530000
IA	41	0-508874	0-5827	0-0	0-0	0-508874	0-250	0-91744
ID	2	10-38400	0-0	0-0	0-0	10-38400	0-5	53-16510
IL	167	0-600000	0-1000	0-800	0-0	0-600000	0-3800	0-184000
IN	134	0-672839	0-250	0-0	0-0	0-672839	0-750	0-120980
KS	27	0-421430	0-1	0-0	0-553	0-421430	0-105	0-72740
KY	43	10-294000	0-61	0-0	0-0	10-294000	0-1580	0-78300
LA	22	0-130000	0-1010	0-0	0-0	0-130000	0-0	0-3600
MA	92	0-219600	0-250	0-9504	0-0	0-219850	0-250	0-152000
MD	28	250-109000	0-0	0-0	0-0	250-109000	0-22	0-62650
ME	17	0-366500	0-0	0-0	0-0	0-366500	0-8800	0-73000
MI	106	0-472418	0-30	0-6	0-0	0-472418	0-10623	0-79000
MN	70	0-211200	0-41	0-0	0-0	0-211200	0-250	0-84250
MO	72	0-427700	0-42	0-4975	0-0	0-427700	0-50	0-153749
MS	37	5-281249	0-1	0-0	0-0	5-281249	0-250	0-52000
NC	133	0-459450	0-250	0-5	0-0	0-459450	0-250	0-115000
ND	4	2500-46250	0-0	0-0	0-0	2500-46250	0-0	0-55300
NE	24	40-227899	0-0	0-0	0-0	40-227899	0-250	0-124344
NH	27	750-141344	0-10	0-0	0-0	750-141344	0-5	0-43400
NJ	86	0-92382	0-153	0-0	0-0	0-92382	0-37	0-75384

Table 5.1 Releases to the Environment from Facilities That Manufcture or Process 1,1,1-Trichloroethane (continued)

		Range of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air	Water	Land	Underground Injection	Total Environment[c]	POTW Transfer	Off-site Waste Transfer
NM	6	0-75304	0-0	0-0	0-0	0-75304	0-0	1180-12440
NV	2	12520-12650	0-0	0-0	0-0	12520-12650	0-0	2200-4770
NY	127	0-581854	0-140	0-4	0-0	0-581854	0-1447	0-400955
OH	226	0-1209014	0-10	0-1806	0-0	0-1209014	0-9541	0-579885
OK	29	0-135000	0-44	0-250	0-0	0-135000	0-3	0-24000
OR	17	750-190000	0-0	0-0	0-0	750-190000	0-0	0-24640
PA	145	0-1183293	0-750	0-2905	0-0	0-1183293	0-750	0-141542
PR	16	0-92700	0-0	0-0	0-0	0-92700	0-1	0-101000
RI	38	81-47192	0-0	0-9100	0-0	81-47192	0-1210	0-52100
SC	52	0-919000	0-12	0-0	0-0	0-919000	0-250	0-86000
SD	8	7345-67267	0-0	0-0	0-0	7345-67267	0-0	0-38400
TN	77	0-323000	0-0	0-250	0-0	0-323000	0-250	0-206345
TX	150	0-715204	0-120	0-14	0-0	0-715204	0-250	0-80095
UT	20	1-1164840	0-0	0-0	0-0	1-1164840	0-5	0-180000
VA	47	0-105950	0-0	0-0	0-0	0-105950	0-7	0-91154
VI	1	6767-6767	3-3	0-0	0-0	6770-6770	0-0	0-0
VT	15	0-59000	0-0	0-6800	0-0	0-59000	0-0	250-25960
WA	30	42-185000	0-5	0-33	0-0	75-185000	0-390	0-193142
WI	111	4-536156	0-11	0-20	0-5	4-536156	0-19000	0-201804
WV	5	15960-92417	0-104	0-200	0-0	15960-92521	0-8	3604-8410

Source: TRI91 1993

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations used
[c]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = Publicly owned treatment works

values registered in the years 1980-1988 shows that 1,1,1-trichloroethane tested positive in 12% of effluent samples with maximum, median, and mean concentrations of 6,500, 8.0, and 171 mg/L, respectively (STORET 1988). 1,1,1-Trichloroethane releases in water, including release to publicly owned treatment works (POTW), from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 1992 are reported in Table 5-l (TR192 1994). According to TR192 (1994), ≈0.01% of the total 1,1,1-trichloroethane environmental release was discharged to environmental waters from manufacturing and processing facilities in the United States in 1992. An additional 118,000 pounds were discharged into waste waters of POTWs. The TRI data should be used with caution since only certain types of facilities were required to report. This is not an exhaustive list. Higher concentrations of 1,1,1-trichloroethane have been found in surface waters near known industrial sources, such as effluent outfalls or disposal sites, compared to the levels found upstream from these sources (see Table 5-2) (Dreisch et al. 1980; Hall 1984; Kaiser and Comba 1986; Kaiser et al. 1983; Wakeham et al. 1983a).

1,1,1-Trichloroethane has been found in samples from four U.S. cities measured in the National Urban Runoff Program (Cole et al. 1984). 1,1,1-Trichloroethane has been found in the effluent from water treatment plants and municipal waste water (Comba and Kaiser 1985; Corsi et al. 1987; DeWees et al. 1992; Feiler et al. 1979; Lue-Hing et al. 1981; McCarty and Reinhard 1980; Namkung and Rittman 1987; Otson 1987; Pincince 1988; Rogers et al. 1987; Vancil et al. 1991; Young 1978; Young et al. 1983).

1,1,1-Trichloroethane can enter groundwater from various sources. Contamination as a result of industrial activity has occurred (Dever 1986; Hall 1984). Leachate from landfills has percolated into groundwater (Barker 1987; Plumb 1987). The measured soil sorption coefficient (K_{oc}) value of 2.02 (Chiou et al. 1980; Gossett 1987) suggests that 1,1,1-trichloroethane released to soil can leach into groundwater. Measurements of 1,1,1-trichloroethane in drinking water from probability-based population studies (Wallace et al. 1984a, 1987a, 1988), indicate the potential for exposure from drinking water.

5.2.3 Soil

1,1,1-Trichloroethane release on land, including underground injection, from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 1992 are reported in

TABLE 5-2. Detection of 1,1,1–Trichloroethane in Water and Sediments

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Surface water:					
Ohio River (Huntington, WV)	1978–1979	22	ND–0.57[a]	NS	Dreisch et al. 1980
Schuylkill Creek (Philadelphia, PA)		33	ND–0.28	NS	
Niagara River	1981	17	ND–0.017[b]	0.007	Kaiser et al. 1983
Lake Ontario		82	ND–0.180	NS	
Lake St. Clair, Canada	1984	64	0–0.112[b]	0.052	Kaiser and Comba 1986
Brazos River, TX	1981–1982	10	ND–0.61[a]	0.1	McDonald et al. 1988
Quinnipiac River (Southington, CT)	1980	5	ND–9.7[a]	2.6	Hall 1984
Valley of the Drums, KT (on-site standing water)	1979	NS	ND–9.4[a]		Stonebraker and Smith 1980
Lang Property, NJ	1985	NS	9[a]		EPA 1987c
Pacific Ocean	1975	NS	0.00062–0.0105[c]		Su and Goldberg 1976
Summit National, OH (NPL site)	1987				EPA 1988n
on-site		3	5–66	13	
off-site		6	ND–29	4.8	
Sediments:					
Lake Pontchartrain, LA	1980	NS	ND–0.01[d]		Ferrario et al. 1985
Pacific Ocean (Los Angeles)	1981	2		<0.5	Young et al. 1983
Detroit River, MI	1982	2	1–2[e]	NS	Fallon and Horvath 1985
Summit National, OH (NPL site) on-site pond sediment	1987	7	50–2,500[f]	670[f]	EPA 1988n

TABLE 5-2. Detection of 1,1,1–Trichloroethane in Water and Sediments (continued)

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Groundwater:					
CERCLA[g] hazardous waste sites	1981–1984	178	NS		Plumb 1987
Landfill Sites, Ontario, Canada	NS	NS	ND–2.8[a]	NS	Barker 1987
Southington, CT	1980	28	ND–11,000[a]	NS	Hall 1984
New Jersey	1980–1982	315	NS	NS	Fusillo et al. 1985
Montgomery County, MD	1983	4	<10–1,600[a]	NS	Dever 1986
Hastings, NE	1984	15	ND–12.1[a]	NS	Fischer et al. 1987
U.S. cities	1981–1982				
Population <10,000 (random samples)		280	ND–18[a]		Westrick et al. 1984
Population <10,000 (nonrandom)[h]		321	ND–8.2		
Population >10,000 (random samples)		186	ND–3.1		
Population >10,000 (nonrandom)[h]		158	ND–21		
Minnesota[i]	1983	20	ND–470[a]	NS	Sabel and Clark 1984
Lang property, NJ	1985	NS	8,200[a]		EPA 1987c
Marshall landfill, CO[j]	1983	NS	ND–350[a]		EPA 1986b
Forest Waste Disposal Site	1983	NS	130[a]		EPA 1986c
Genesee County, MI[j]					
Palmer, MA PSC Resources, Inc. (NPL site)	1987	NS			Massachusetts Department of Public Health 1989
on-site			NS	40,000[m]	
off–site			NS	3,700[m]	
Idaho National Eng. Lab, IO	1987	112	ND–140[a]		Mann and Knobel 1988

TABLE 5-2. Detection of 1,1,1–Trichloroethane in Water and Sediments (continued)

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Drinking water:					
Old Love Canal, NY	1978	9	0.010–0.120[b]		Barkley et al. 1980
Bayonne/Elizabeth, NJ	1980				Wallace et al. 1984a
home		75	0.03–3.50[k]	0.02	
work		45	0.02–1.60	0.07	
Research Triangle Park, NC					
home		30	0.02–1.90		
work		18	0.02–0.89		
New Jersey	1981		NS–5.3	0.6	Wallace et al. 1987a
	1982		NS–2.6	0.2	
	1983		NS–1.6	0.2	
North Carolina	1982		NS–0.05	0.03	
North Dakota	1982		NS–0.07	0.04	
Los Angeles, CA	February 1984	117	NS	0.15[a]	Wallace et al. 1988
Los Angeles, CA	June 1984	52	NS	0.08[a]	
Contra Costa, CA	May 1984	71	NS	0.09[a]	
Drinking water wells (groundwater):					
Maine	NS	NS	NS–5,440	NS	Burmaster 1982
New York			NS–5,100		
Connecticut			NS–1,600		
New Jersey			NS–965		

TABLE 5-2. Detection of 1,1,1–Trichloroethane in Water and Sediments (continued)

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Nassau County, NY			NS–310	9	
Suffolk County, NY					
public wells	1976–1986	575	NS–900[a]	16.5	Zaki 1986
private wells		19,000	NS–12,200	23.8	
Wisconsin	1980–1984				Krill and Sonzogni 1986
community wells		1,174	NS		
private wells		617	NS		
Rock River Terrace, IL[j]	1985	NS	NS–3.2		EPA 1986d
South Brunswick, NJ	1977	NS	150–1,500		Althoff et al. 1981
Sewage Sludge					
United States (Site NS)	1978	2	23–99[a]		Feiler et al. 1980
Forest Wate Disposal Site, MI[j]	1983	NS	25[a]		EPA 1986c
Vestal, NY[j]	1985–1986	2	25–47[a]	36[a]	ATSDR 1988
Urban runoff:					
Washington, DC; Denver, CO	NS–1982	NS	1.6–10[a]	NS	Cole et al. 1984
Rapid City, SD					
Lake Quinsigamond, MA					
Rain:					
Los Angeles, CA	1982	1		0.069[b]	Kawamura and Kaplan 1983
Beaverton, OR	1982	21	0.128–0.924[l]	0.434	Rasmussen et al. 1983

TABLE 5-2. Detection of 1,1,1–Trichloroethane in Water and Sediments (continued)

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Snow:					
Mt. Hood, OR	1981–1982	25	0.063–0.128[l]	0.091	Rasmussen et al. 1983
California	1975	2	0.0006–0.0062[c]		Su and Goldberg 1976
Alaska		1	0.027		

[a]Data reported in µg/L; converted to ppb using the conversion factor 1 ppb = 1 µg/L
[b]Data reported in ng/L; converted to ppb using the conversion factor 1 ppb = 1,000 ng/L
[c]Data reported in pg/mL; converted to ppb using the conversion factor 1 ppb = 1,000 pg/mL
[d]Data reported in ng/g; converted to ppb using the conversion factor 1 ppb = 1 ng/g
[e]Data reported in mg/kg; converted to ppb using the conversion factor 1 ppb = 0.001 mg/kg
[f]Data reported in µg/kg; converted to ppb using the conversion factor 1 ppb = 1 µg/kg
[g]Comprehensive Emergency Response, Compensation, and Liability Act
[h]Nonrandom sites were chosen by states/municipalities in an attempt to identify problem areas.
[i]Site near municipal solid waste site
[j]NPL site
[k]Data reported in ng/mL; converted to ppb using the conversion factor 1 ppb = 1 ng/mL
[l]Data reported in ppt; converted to ppb using the conversion factor 1 ppb = 1,000 ppt
[m]Data reported in ppm; converted to ppb using the conversion factor 1 ppb = 0.001 ppm

ND = not detected; NS = not specified

Table 5-l (TRI92 1994). According to TRI92 (1994), an estimated total of ≈76,000 pounds of 1,1,1-trichloroethane, amounting to ≈0.07% of the total environmental release, was discharged to the land from manufacturing and processing facilities in the United States in 1992. The TRI data should be used with caution since only certain types of facilities were required to report. This is not an exhaustive list.

Data on soil contamination by 1,1,1-trichloroethane are lacking in the literature, which is what one would expect based on the TRI92 (1994) data given in Table 5-1. Contamination of soil is possible by direct application of insecticides and rodenticides that contain 1,1,1-trichloroethane as a solvent. Land application of sewage sludge at typical application rates may slightly elevate the level of 1,1,1-trichloroethane in agricultural soil, but the level is not expected to be of environmental concern in the majority of cases (Wilson et al. 1994). The most likely routes for soil contamination are through accidental spills, the contamination of soil by landfill leachates, leaching of contaminated surface waters from treatment/storage lagoons, wet deposition, and possibly by the percolation of contaminated rainwater through soil.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

1,1,1-Trichloroethane is a volatile organic compound with moderate water solubility (1,500 mg/L at 25 ºC) (Horvath 1982). The experimental Henry's law constants measured for this compound range from $6.3x10^{-3}$ to $17.2x10^{-3}$ atm m^3/mol at 25 ºC (Chiou et al. 1980; Gossett 1987; Tse et al. 1992); this suggests that volatilization from water should be the dominant fate process. Volatilization of 1,1,1-trichloroethane from water has readily occurred in the laboratory, in the field, and during waste water treatment (Dilling 1977; Dilling et al. 1975; Kincannon et al. 1983b; Piwoni et al. 1986; Wakeham et al. 1983b). Volatilization of 1,1,1-trichloroethane also has occurred from soil and from the groundwater of unconfined aquifers to the soil (Kreamer 1984; Piwoni et al. 1986).

Based on the experimental values for the log octanol/water partition coefficient (K_{ow}), 2.49 (Hansch and Leo 1985), and log K_{oc}, in the range of 2.02-2.26 (Chiou et al. 1979; Friesel et al. 1984; Park and Lee 1993), 1,1,1-trichloroethane would be expected to show high mobility in soil and readily leach into groundwater (Lyman et al. 1990; Swarm et al. 1983). In surface waters, 1,1,1-trichloroethane

would not be expected to show appreciable adsorption to sediment or suspended organic material. An experimental bioconcentration factor (BCF) of 9 (bluegill sunfish) has been determined for 1,1,1-trichloroethane (Barrows et al. 1980), suggesting that in fish and other aquatic organisms, uptake from water should not be an important fate process.

1,1,1-Trichloroethane has a vapor pressure of 123 mm Hg at 20 ºC (see Table 3-2), which means that it exists in the vapor phase in the atmosphere (Eisenreich et al. 1983). Since this compound has moderate water solubility (see Table 3-2), vapor phase 1,1,1-trichloroethane will be removed from the air via washout by rain and transported to the terrestrial surface. It has been identified in rainwater (Jung et al. 1992; Kawamura and Kaplan 1983; Pluemacher and Renner 1993; Rasmussen et al. 1983). 1,1,1-Trichloroethane removed by rain water would be expected to re-volatilize rapidly to the atmosphere. Because of its long half-life of ≈4 years in the atmosphere (see Section 5.3.2.1), tropospheric 1,1,1-trichloroethane will be transported to the stratosphere, where it will participate in the destruction of the ozone layer. It will also undergo long-distance transport from its sources of emissions to other remote and rural sites. This is confirmed by the detection of this synthetic chemical in forest areas of Northern and Southern Europe and in remote sites (Ciccioli et al. 1993).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The dominant atmospheric fate process for 1,1,1-trichloroethane is predicted to be degradation by interaction with photochemically-produced hydroxyl radicals. Earlier experimental rate constants for this gas-phase reaction ranged from $2.8x10^{-14}$ to $1.06x10^{-14}$ cm^3/mol-sec (20-30 ºC) (Butler et al. 1978; Chang and Kaufman 1977; Cox et al. 1976; Crutzen et al. 1978; Howard and Evenson 1976; Jeong et al. 1984). More recent work indicates that this rate constant ranges from $0.95x10^{-14}$ cm^3/mol-sec to $1.2x10^{-14}$ cm^3/mol-sec (Finlayson-Pitts et al. 1992; Jiang et al. 1992; Lancar et al. 1993; Talukdar et al. 1992). 1,1,1-Trichloroethane is degraded via H-atom abstraction to $CCl_3CH_{2/}$ and reacts with O_2 to yield the peroxy radical ($CCl_3CH_2O_{2/}$) (DeMore 1992; Spence and Hanst 1978). Using an estimated atmospheric hydroxyl radical concentration of $5.0x10^5$ mol/cm^3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ≈6 years. The estimated atmospheric lifetime of 1,1,1-trichloroethane, which incorporates all removal processes, was also estimated to be

≈6 years (Prinn et al. 1987; Prinn et al. 1992). This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with OH radicals.

Photolytic degradation experiments have been performed in the presence of NO and NO_2; 1,1,1-trichloroethane underwent <5% degradation in 24 hours in the presence of NO (Dilling et al. 1976). In a smog chamber experiment in the presence of No_x, 1,1,1-trichloroethane showed a disappearance rate of 0.1% per hour (Dimitriades and Joshi 1977). Other studies have also concluded that 1,1,1-trichloroethane has low potential to form ozone as a result of photochemical reaction in the presence of NO_x (Andersson-Skoeld et al. 1992; Derwent and Jenkin 1991).

Under laboratory conditions thought to mimic atmospheric smog conditions, direct photochemical irradiation of 1,1,1-trichloroethane in the presence of elemental chlorine was performed. 1,1,1-Trichloroethane was the least reactive and thus the most stable of all chloroethanes under these conditions (Spence and Hanst 1978).

Direct photochemical degradation of 1,1,1-trichloroethane in the troposphere is not expected to be an important fate process, because there is no chromophore for absorption of ultraviolet light (>290 nm) found in sunlight at tropospheric altitudes (Hubrich and Stuhl 1980; VanLaethem-Meuree et al. 1979). A laboratory experiment performed in sealed Pyrex ampules showed loss of 1,1,1-trichloroethane in 2 weeks under the influence of sunlight; however, catalysis by the Pyrex surface was probably responsible for the enhanced reactivity (Buchardt and Manscher 1978).

The relatively long tropospheric residence time for 1,1,1-trichloroethane suggests that migration to the stratosphere should be important. An estimated 11-15% of 1,1,1-trichloroethane released to the atmosphere is expected to survive and migrate to the stratosphere (Prinn et al. 1987; Singh et al. 1992). In the stratosphere, chlorine atoms produced from 1,1,1-trichloroethane by ultraviolet light may interact with ozone contributing to the destruction of the stratospheric ozone layer. Compared to CFC- 11 (trichlorofluoromethane), the steady state ozone depletion potential of 1,1,1-trichloroethane has been estimated to be 0.1-0.16 (Gibbs et al. 1992; Solomon and Albritton 1992).

5.3.2.2 Water

Slow biodegradation of 1,1,1-trichloroethane can occur under both anaerobic and aerobic conditions. Anaerobic degradation of 1,1,1-trichloroethane is thought to occur predominantly through reductive dechlorination by methane-producing bacteria (Vargas and Ahlert 1987; Vogel and McCarty 1987) and by sulfate-reducing organisms (Cobb and Bouwer 1991; Klecka 1990). Determined experimental halflives for anaerobic degradation using mixed culture bacteria ranged from 1 day to 16 weeks in the laboratory (Bouwer and McCarty 1983a, 1984; Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987; Wood et al. 1985); based on a study from an injection well, after 3 months of injection, the predicted half-life of 1,1,1-trichloroethane in an aquifer was 200-300 days (Bouwer and McCarty 1984). Results obtained in a grab sample study of an aquifer suggest that anaerobic biodegradation of 1,1,1-trichloroethane will not occur (Wilson et al. 1983); however, the spiked concentration of 1,1,1-trichloroethane in the study, 1 mg/L, was in a range determined to be toxic to microorganisms (Barth and Bunch 1979; Benson and Hunter 1977; Vargas and Ahlert 1987). Another grab sample study, performed using more realistic concentrations, indicates that 1,1,1-trichloroethane slowly degrades under anaerobic conditions to 1,1-dichloroethane in groundwater (Parsons and Lage 1985; Parsons et al. 1985). However, when mixed anaerobic cultures were provided with acetate as primary substrate, the biodegradation of secondary substrate 1,1,1-trichloroethane occurred even without acclimation at concentrations exceeding 1 mg/L (Hughes and Parkin 1992). A laboratory study showed that anaerobic biodegradation of 1,1,1-trichloroethane did not occur under denitrification conditions even after 8 weeks of incubation (Bouwer and McCarty 1983b).

Aerobic biodegradation in surface water and groundwater is not likely to be an important fate process since experimental studies did not indicate significant aerobic degradation of 1,1,1-trichloroethane (Mudder and Musterman 1982; Klecka et al. 1990; Nielson et al. 1990; Wilson and Pogue 1987). One interesting study showed that 1,1,1-trichloroethane underwent aerobic degradation in the presence of Fe^{+2}/porphyrin solution (82% in 21 days), thought to be a catalyzed reductive chlorination (Klecka and Gonsior 1984). It is difficult to interpret these results in terms of the potential for environmental significance. One study reported that 1,1,1-trichloroethane underwent moderate biodegradation with significant concomitant volatilization (Tabak et al. 1981); however, experimental details are not sufficient to rule out loss due solely to volatilization. Halogenated aliphatic hydrocarbons, including 1,1,1-trichloroethane, act as cometabolic substrates for certain aerobic chemotrophs. In such cases, the organisms grow on another substrate and the enzymes induced under the particular growth conditions

fortuitously biodegrade the halogenated aliphatics (Leisinger 1992). Such aerobic biodegradation of, 1,1,1-trichloroethane up to a concentration of 1.2 mg/L was observed with methane-oxidizing (methanotrophic) bacteria isolated from an aquifer (Arvin 1991).

Anaerobic biodegradation proceeds via reductive dechlorination (Leisinger 1992; McCarty 1993). The major product from the anaerobic degradation of 1,1,1-trichloroethane has been identified as 1,1-dichloroethane, which slowly degrades to chloroethane in a secondary reaction (Hallen et al. 1986; Vogel and McCarty 1987). Therefore, total biodegradation of 1,1,1-trichloroethane is feasible by combining anaerobic dehalogenation with subsequent aerobic treatment (Leisinger 1992). Aerobic biodegradation of 1,1,1-trichloroethane, on the other hand, proceeds via substitutive and oxidative mechanisms with the production of trichloroethyl alcohol, which is further oxidized to chloride, carbon dioxide and water (McCarty 1993).

Products from the abiotic degradation of 1,1,1-trichloroethane have also been identified. Acetic acid can arise from the hydrolysis of 1,1,1-trichloroethane (calculated half-life of 1.2 years at 2.5 ºC and pH 7). Elimination of HCI can produce 1,1-dichloroethene (Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987). The calculated half-life for this reaction is 4.8 years at 25 ºC and pH 7 (Ellenrieder and Reinhard 1988). The half-lives of abiotic degradation of 1,1,1-trichloroethane by reaction with nucleophiles, such as HS^- and S_2O_2 which might be present in water, should be insignificant compared to the other processes described (Haag and Mill 1988). A 2.8 mmol aqueous solution of 1,1,1-trichloroethane reacted with ozone (concentration 1 mg/L) with a half-life of >32 days at 22 ºC and a pH of 7 (Yao and Haag 1991). Therefore, reaction with ozone will not be an important process for the transformation of 1,1,1-trichloroethane present in natural bodies of water.

5.3.2.3 Sediment and Soil

Data are lacking on the degradation of 1,1,1-trichloroethane in soil. In a grab sample experiment, anaerobic degradation of 1,1,1-trichloroethane occurred slowly in soil (16% in 6 days) (Henson et al. 1988). If the microorganisms in the soil were first activated by using methane as a nutrient source, 46% of 1,1,1-trichloroethane degraded during the same period under aerobic conditions (Henson et al. 1988). Incubation of 1,1,1-trichloroethane in soil under aerobic conditions resulted in no measurable biodegradation (Klecka 1990).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

1,1,1-Trichloroethane has been identified in urban, rural, and indoor air throughout the United States at concentrations shown in Table 5-3. Due to the nature of 1,1,1-trichloroethane's use, volatilization to the atmosphere is a predictable outcome, and thus its widespread detection is not unexpected. It is the only chlorinated ethane regularly seen as a background pollutant in the troposphere (Spence and Hanst 1978). For the year 1980, an estimated global atmospheric quantity of 1,1,1-trichloroethane, based on absolute concentrations obtained over a 3-year period, was 2.58×10^9 kg (5,690 million pounds) (Prinn et al. 1983). An estimated average concentration of 0.14 ppb in 1980, based on a characterization of its sources, abundance, and atmospheric sinks, was also reported (Ramanathan et al. 1985). Recent data indicate that the average atmospheric concentration of 1,1,1-trichloroethane was 0.13 ppb for the middle of 1988 (Khalil and Rasmussen 1989). Based on absolute concentrations obtained over a 12-year period, a global atmospheric concentration of 157 ppt (0.157 ppb) was estimated for 1,1,1-trichloroethane in the middle of 1990 (Prinn et al. 1992). Atmospheric measurements at several surface stations made between 1978 and 1990 indicated that the global average concentration of 1,1,1-trichloroethane increased at a rate of 4.4±0.2% over this time period (Prinn et al. 1992).

The measured concentration of 1,1,1-trichloroethane in urban air usually ranges from 0.1 to 1 ppb; however, levels <1,000 ppb have been observed in large urban areas or near hazardous waste sites. Representative monitoring data on the concentration of 1,1,1-trichloroethane in air can be found in Table 5-3. Rural levels of 1,1,1-trichloroethane are typically <0.2 ppb. The long atmospheric lifetime of 1,1,1-trichloroethane allows the compound to be carried a considerable distance from its initial point of release; detectable levels have been measured in numerous remote areas throughout the world and are shown in Table 5-3 (Class and Ballschmiter 1986; DeBortoli et al. 1986; Guicherit and Schulting 1985; Hov et al. 1984; Ohta et al. 1976; Rasmussen et al. 1982). The mean background concentration of 1,1,1;trichloroethane over subarctic North America in the summer of 1990 was 0.155 ppb (Wofsy et al. 1994). During a period of arctic haze, the concentration of 1,1,1-trichloroethane in the polluted arctic air was 2-15% higher than in clean air over the arctic (Khalil and Rasmussen 1993).

The concentration of 1,1,1-trichloroethane in indoor air is variable, and seems to depend on individual practices, season, outdoor concentration, age of building, and building air-exchange characteristics

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
Urban air:					
El Monte, CA	1982–1983	NS	0.8–6.6[a]	2.1	Shikiya et al. 1984
Los Angeles, CA	1983		0.8–2.4	NS	
Dominguez Hills, CA			0.6–2	NS	
Riverside, CA			0–0.8	NS	
Research Triangle Park, NC	1980	61	0.0024–43.7[b]	0.83	Wallace et al. 1984a
Houston, TX	1980		0.134–1.499[c]	0.353	Singh et al. 1992
St. Louis, MO			0.132–0.896	0.235	
Denver, CO			0.171–2.699	0.713	
Riverside, CA			0.205–1.349	0.747	
Staten Island, NY	1981		0.221–1.427	0.468	
Pittsburgh, PA			0.158–1.595	0.486	
Chicago, IL			0.241–0.909	0.476	
Iberville Parish, LA	1977	11	ND–1.61[b]	0.31	Pellizzari 1982
Kib–Buc Diposal Site, NJ	1977	4	ND–22.0		
Rutherford, NJ	1978	150	ND–6.3	0.17	Bozzelli and Kebbekus 1979
Rutherford, NJ (North)		29	ND–3.6	0.55	
Rutherford, NJ (Clifton)		26	ND–trace		
Newark, NJ		110	ND–7.8	0.39	
Bridgewater, NJ		22	ND–0.83	0.05	
Los Angeles Basin	1972	59	0.01–2.30	0.37	Simmonds et al. 1974
Los Angeles, CA	1984	23	NS–3.70	0.74	Pellizzari et al. 1986
Los Angeles, CA	1979		0.224–5.144[c]	1.028	Singh et al. 1981
Phoenix, AZ			0.197–2.813	0.823	
Oakland, CA			0.142–0.967	0.290	
New Jersey					
fall (day)	1981	86	ND–86[b]	0.60[d]	Wallace et al. 1985, 1987a;
fall (night)		86[e]	ND–7.3	0.68	Hartwell et al. 1984b
summer	1982	60		0.93	
winter	1983	8		0.26	
Bozeman, MN	1976[e]	1	0.15		Taketomo and Grimsrud 1978
Seagirt, NJ	1974	NS	0.044–0.20	0.10	Lillian et al. 1975

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air (continued)

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
New York, NY			0.10–1.6	0.61	
Sandy Hook, NJ			0.030–0.330	0.15	
Delaware City, DE			0.03–0.30	0.10	
Baltimore, MD			0.044–0.21	0.12	
Wilmington, OH			0.030–0.35	0.097	
Bayonne, NJ	1973		0.075–14.4	1.59	
Greensboro, NC	1982	32		11.1[b]	Wallace et al. 1987a
Devils Lake, ND		24		0.009[b]	
La Jolla, CA	1974–1976	23	0.13–1.1	0.00037	Su and Goldberg 1976
California coast (marine air)	1974	5	0.14–0.30	0.00019	
Washington, DC	1974	1	0.5		
Los Angeles (Chinatown), CA	1974	1	3.4		
Santa Monica, CA	1974	1	1.3		
Orange County, CA	1974	3	0.37–0.68		
Chicago, IL	1974	2	0.37–0.68		
Greensboro, NC	1980	20	NS–9.81[b]	0.33	Hartwell et al. 1984a
Baton Rouge, LA	198	127	NS–13.5	0.11	Pellizzari et al. 1984a, 1986
Houston, TX	1981	11	NS–1.41	0.47	
Bayonne/Elizabeth, NJ	1980	165	0.133–131[b]		Wallace et al. 1984a
Bayonne/ELizabeth, NJ	1981	80–90	NS–87[b]	1.68	Wallace et al. 1985
Chicago, IL	1986–1990	103	NS	0.61[b]	
St. Louis, IL		83		0.72[b]	Sweet and Vermette 1992
Hawthorne, CA	1987–1990	NS	0.8–7.0	NS	Hisham and Grosjean 1991
			0.8–18.0		
Long Beach, CA			2.2–14.7		
			2.2–9.9		
Anaheim, CA			0.5–8.5		
			13.2–22.2		
Los Angeles, CA			2.7–6.3		
			8.3–14.0		
Burbank, CA			1.2–6.1		
			7.1–28.4		
Azusa, CA			3.2–17.1		

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air (continued)

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
Claremont, CA			3.3–15.0		
Los Angeles, CA			1.7–6.5		
Ventura, CA			0.5–2.7		
West Los Angeles, CA			1.6–2.2		
Los Angeles, CA (UCLA)			0.5–0.9		
Malibu, CA			0.5–1.6		
Northeast Los Angeles, CA			0.8–7.2		
Burbank, CA			0.5–5.7		
			0.13–1.17		
Los Angeles, CA	February 1984	24	NS	6.3[b]	Wallace et al. 1988
Los Angeles, CA	May 1984	23		1.1[b]	
Contra Costa, CA	June 1984	10		0.52[b]	
Hawthorne, CA	1987–1990	NS	NS		Hisham and Grosjean 1991
fall				12.9	
summer				3.4	
Long Beach, CA					
fall				6.3	
summer				8.5	
Anaheim, CA					
fall				16.9	
summer				3.0	
Los Angeles, CA					
fall				9.9	
summer				4.5	
Burbank, CA					
fall				18.5	
summer				3.1	
Washington, DC	1989	5	0.28–0.42[b]	0.35[b]	EPA 1990b
Los Angeles, CA (winter)	1987	51	NS	1.09[b,f]	Hartwell et al. 1992
Rural air:					
Pullmam, WA	1974–1975	NS	NS	0.100[c]	Grimsrud and Rasmussen1975
Eastern WA	1976	389	0.090[c]–0.18	0.135	Cronn et al. 1983
Stanford Hills, CA	1975	75		0.0776[c]	Singh et al. 1977

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air (continued)

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
Point Reyes, CA		300	NS	0.0903	
Pacific NW, USA	1975			0.087[c]	Rasmussen et al. 1981
	1976			0.098	
	1977			0.107	
	1978			0.117	
	1979			0.135	
	1980			0.156	
Antarctica	1975			0.045	
	1976			0.057	
	1977			0.070	
	1978			0.085	
	1979			0.095	
	1980			0.102	
Pt. Barrow, AL	1980–1982	NS	0.150–0.172[c]	0.152 (0.168)[g]	Khalil and Rasmussen 1983
Midland, MI	1975	7	0.0916–0.188[h]	0.104	Russell and Shadoff 1977
Old Love Canal, NY	1978	9	ND–0.989[h]		Barkley et al. 1980
White Face Mountains, NY	1974	NS	0.032–0.13	0.067	Lillian et al. 1975
Mt Hood, OR	1981–1982	7	0.104–0.179	0.156	Rasmussen et al. 1983
Beaverton, OR	1982	7	0.154–0.363	0.202	
Mt. Cuyamaca, CA	1975	1		0.41	Su and Goldberg 1976
Montgomery Pass, NE				10.34	
Lytton Lake, CA				10.07	
Champain, IL	1986–1990	23	NS	0.2[b]	Sweet and Vermette 1992
Chattanooga, TN	1986–1987	30	0.18–9.6[b]	3.98[b]	Parkhurst et al. 1988
San Nicolas Island, CA	1987	NS	0.55–0.57	NS	Hisham and Grosjean 1991
Kanawha Valley, WV	NS[e]			353.6[b]	Cohen et al. 1989
Indoor Air:					
Old Love Canal, NY	1978	9	ND–0.220[h]	14	Barkley et al. 1980
Bozeman, MN	NS[e]	8	0.12–0.73		Taketomo and Grimsrud 1978
Greensoro, NC	1980	20	NS–28.7[b]	1.15	Hartwell et al. 1984a; Pellizzari et al. 1986
Baton Rouge, LA	1981	27	NS–45.0	0.28	
Houston, TX	1981	11	NS–5.73.7		

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air (continued)

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
Elizabeth/Bayonne, NJ	1981	25	NS–163[b]	2.96	Pellizzari et al. 1986
	1982	71	NS–22.2	1.83	
	1983	9	NS–31.53.7		
Los Angeles, CA					
winter	1984	25	NS–37.0	4.44	
summer	1984	23	NS–17.4	1.46	
Antioch–W. Pittsburgh, CA					
Public access buildings	1984	16	NS–2.590.78		Wallace et al. 1987c
Recently constructed building after occupancy	1983–1985	70.55–7.5[b]	0.36–18.3		
Elderly home		30.73–69.6			
	NS	NS	0.12–22.6	NS	Pellizzari et al. 1984b
Los Angeles, CA	1987	51			Hartwell et al. 1992
kitchen			NS	1.78[b,f]	
living area			NS	2.33[b,f]	
Chattanooga, TN	1986				Parkhurst et al. 1988
residential		34	0.37–37[b]	5.1[b]	
public buildings		37	0.92–50[b]	13[b]	
Dallas, TX					Gallagher and Kurt 1990
incubator air in an intensive care nursery	1988		460,000–160,000[l]	95,000[l]	
Washington DC, U.S. EPA headquarters:	1989				EPA 1990b
Waterside Mall		51	0.42–4.8[b]	1.6[b]	
Crystal City		5	0.56–0.70[b]	0.61[b]	
Fairchild		5	1.2–1.3[b]	1.2[b]	
Neenah, WI, telephone switching office	1987			0.17[b]	Shields and Weschler 1992
second floor break room		NS	NS	0.11[b]	
second floor break room		1	NS	0.056[b]	
		NS	NS	0.26[b]	
		1	NS		
Southern California museums	1986				Hisham and Grosjean 1991
El Pueblo			1.2–5.1	NS	
LACMA			2.9–3.9	NS	
Page			>30	NS	
Getty			3.7–4.8	NS	
Southwest			2.2–7.3	NS	

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air (continued)

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
Personal air:					
Chapel Hill, NC	1978		172.65–19.6[b]	15.0	Zweidinger et al. 1983
Beaumont, TX		11	1.51–196	33	Wallace et al. 1982
New Jersey	1981	346–48	ND–6,040[b]	3.5[d]	Wallace et al. 1987a
fall (day)					
New Jersey					Wallace et al. 1985
fall (night)		339–41	ND–1520	3.5	
fall (summer)	1982	148		1.7[d]	
winter	1983	48		4.0	
Bayonne/Elizabeth, NJ	1980	165 (9)	0.13–130[b]	1.7	Wallace et al. 1984a
Research Triangle Park, NC		61 (3)	0.024–43.2	0.82	
Bayonne/Elizabeth, NJ	1981	339–348	NS–61,100	22.2	Wallace et al. 1984b, 1985
Devils Lake, ND	1982	24	[b]	4.63[b]	Wallace et al. 1987a
Greensboro, NC	1982	32	[b]	5.92[b]	
Los Angeles, CA	February 1984	110	NS	17.8[b]	Wallace et al. 1988
Los Angeles, CA	May 1984	50	NS	8.1[b]	
Contra Costa, CA	June 1984	67	NS	2.9[b]	
Los Angeles, CA	1987	51	NS	2.6[b,f]	Hartwell et al. 1992
Near waste/landfill site:					
Hamilton, OH	1983	NS	0.36–23.8[b]	NS	Levine et al. 1985
Elizabeth, NJ	1980	NS	ND–330	NS	
New Jersey (NPLHS)	1983				
Site A		24	ND–4.49	0.38	Laregina et al. 1986
Site B		15	ND–1.84	0.51	Harkov et al. 1985
Site C		14	ND–18.97	3.04	
Site D		14	ND–2.89	0.57	
Site E		15	ND–1.22	0.84	
Landfill LF		15	ND–7.15	1.29	
New Jersey	1976	4	ND–22.2	9.0	Pellizzari 1982
California	1984–1986	NS	ND–3,600[j]	NS	Wood and Porter 1987

TABLE 5-3. Detection of 1,1,1-Trichloroethane in Air (continued)

Media type/location	Sampling dates	Number of samples	Concentration		Reference
			Range	Mean	
Stanislaus County, CA	1987				Hodgson et al. 1992
on site		NS	<10–13,000	NS	
outside (nearby residential home)		NS	NS	0.3	
inside (nearby residential home [basement])		NS	NS	0.7	
20 Class II landfills:					
Long Island, NY	1982				Walsh et al. 1988
on site			140[l]		
nearby residential homes			1		
nearby school			1		

[a]Monthly mean
[b]Data reported in µg/m^3; converted to ppb using the conversion factor 1 ppb = 5.4 µg/m^3
[c]Data reported in ppt; converted to ppb using the conversion factor 1 ppb = 1,000 ppt
[d]Weighted geometric mean
[e]Date of study not given
[f]Data reported as median
[g]Summer (winter)
[h]Data reported in ng/m^3; converted to ppb using the conversion factor 5,400 ng/m^3 = 1 ppb
[l]Data reported in ppm; converted to ppb using the conversion factor 0.001 ppm = 1 ppb

ND = not detected; NS = not specified

(Cohen et al. 1989; Hartwell et al. 1987a, 1987b;1992; Hisham and Grosjean 1991; Lioy et al. 1991; Wallace 1986; Wallace et al. 1986a, 1986b, 1988, 1989, 1991). For example, college students monitored simultaneously on the same campus were found to have levels of personal exposure varying by as much as two orders of magnitude (Wallace et al. 1982; Zweidinger et al. 1983). Further, two studies suggest that buildings with air conditioning may have higher levels of 1,1,1-trichloroethane in indoor air (Cohen et al. 1989; Hisham and Grosjean 1991). 1,1,1-Trichloroethane has been found at levels ≤70 ppb in newly constructed buildings (Wallace et al. 1987b). The concentration of 1,1,1-trichloroethane in new and recently renovated buildings was as high as 290 ppb (Rothweiler et al. 1992). New carpet and other new building materials that contain 1,1,1-trichloroethane may be responsible for higher levels in new and renovated buildings. During normal periods (no renovation or construction), the levels of total volatile organics are inversely proportional to the air exchange rate of the building (Shields and Weschler 1992). Higher levels of 1,1,1-trichloroethane are expected to be found in indoor air during winter than any other season (Wallace et al. 1991). The effect of outdoor air on indoor air was demonstrated by the detection of higher levels of 1,1,1-trichloroethane during outdoor stagnation conditions when the levels were higher compared to levels under non-stagnation conditions (Lioy et al. 1991). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3-4.4 ppb and outdoor concentrations of 0.11-0.92 ppb (Pellizzari et al. 1986). Recent studies have determined the presence of 1,1,1-trichloroethane in products expected to be in most households (Section 5.5) (Frankenberry et al. 1987; Maklan et al. 1987; Sack et al. 1992; Spicer et al. 1987).

5.4.2 Water

1,1,1-Trichloroethane has been identified in surface water, groundwater, drinking water, effluent, rain, snow, and urban runoff. The amount of the chemical detected in surface and groundwater depends upon the location of the sampling point. Concentrations in surface water removed from point-source emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <l ppb. In random samples of groundwater taken in the United States, concentrations have ranged from 0 to 18 ppb. Groundwater samples obtained near sources of release to soil or the ground have been as high as 11,000 ppb. Drinking water from surface or groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01 to 3.5 ppb.

Data on the occurrence of 1,1,1-trichloroethane in water are presented in Table 5-2. Data on the concentration of 1,1,1-trichloroethane in effluent can be found in Table 5-4.

1,1,1-Trichloroethane was found in groundwater at hazardous waste sites in 18.9% of 178 sites from the CERCLA database (Comprehensive Emergency Response, Compensation and Liability Act), making it the seventh most frequently detected compound in this study (Plumb 1987). It was found in water samples from 42 of 357 Contract Laboratory Program (CLP) sites; the concentration range of the mean values was 1.75-1,100 ppb (Viar 1987).

5.4.3 Sediment and Soil

Monitoring data on the occurrence of 1,1,1-trichloroethane in soil are not as extensive as for water or air, which precludes an estimate of typical levels found in soil. The reported levels of 1,1,1-trichloroethane in soils are shown in Table 5-5. In two grab soil samples taken in 1980 from two former sludge lagoons of a solvent recovery operation at Southington, Connecticut, the measured concentrations of 1,1,1-trichloroethane were 23,000 and 120,000 ppb (Hall 1984). The limited data on the concentration of 1,1,1-trichloroethane in soil may be due to its rapid volatilization from soil, its ability to leach through soil, or both. 1,1,1-Trichloroethane has been detected in 696 of 1,408 NPL sites (HazDat 1994). The concentrations of 1,1,1-trichloroethane in sediments are shown in Table 5-2. The mean concentration of 1,1,1-trichloroethane in sediments from a river passing through an industrial area in Japan was 0.4 ppb, although it was not detected in the river water or in the sediment of a river passing through a non-industrial area (Grotoh et al. 1992).

5.4.4 Other Environmental Media

Limited data on the occurrence of 1,1,1-trichloroethane in other media were located. 1,1,1-Trichloroethane has been found in raw, processed, and prepared food products. These data are presented in Table 5-6. 1,1,1-Trichloroethane has been found in fish and shrimp taken from the Pacific Ocean at average concentrations of 2.7 and <0.3 ppm, respectively (Young et al. 1983). It has also been detected in clams and oysters from Lake Pontchartrain, Louisiana, with mean concentrations ranging from 39 to 310 ppm (Ferrario et al. 1985) and from a polluted river in Japan at concentrations ranging from 0.6 to 1.8 ppb wet weight (wt/wt) (Grotoh et al. 1992).

TABLE 5-4. Detection of 1,1,1-Trichloroethane in Effluent

Median type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Industrial waste water:					
Textile plants	1975	64	2–300[a]	NS	Rawlings and Deangelis 1979
Municipal waste water					
Los Angeles, CA	1978	NS			
primary				340[a]	Young 1978
secondary				<10	Young et al. 1983
Los Angeles County, CA					
primary				130	
secondary				180	
Orange County, CA					
primary				4,000	
secondary				<10	
San Diego, CA					
primary				68	
Water factory 21					
influent	1976	50	<0.3–38[a]	4.794	McCarty and Reinhard 1980
Orange County, CA					
effluent		51	0.1–1.2	0.07	
influent	1978	28	0.3–15	2.9	
effluent		17	<0.1–41	0.14	
Chicago, IL, Calumet plant					
influent	1980	2		14[a]	Lue-Hing et al. 1981
effluent				<10	
John Egan plant					
influent		1		11	
effluent				<10	

TABLE 5-4. Detection of 1,1,1-Trichloroethane in Effluent (continued)

Median type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Denver, CO					
reuse influent	1985–1986	14	1.70–6.9[a]	3.74	Rogers et al. 1987
Landfill leachates:					
Collegeville, PA[b]	1983[c]	NS	1–60	NS	Varma 1985
Minnesota[d]	1983	6	ND–7.6[a]		Sabel and Clark 1984
Nuclear power plant emissions:					
Denver, CO					Sturges and Taylor 1990
downwind	1989	6	0.06–0.623[e]	0.27[e]	
upwind		8	0.088–0.251[e]	0.137[e]	

[a]Data reported in µg/L; converted to ppb using the conversion factor 1 ppb = 1 µg/L
[b]National Priority Hazardous Waste Site
[c]Date of study not given
[d]Municipal Solid Waste site
[e]Data reported in ppt; converted to ppb using the conversion factor 1 ppb = 1,000 ppt

ND = not detected; NS = not specified

TABLE 5-5. Detection of 1,1,1-Trichloroethane in Soils

Media type/location	Sampling dates	Number of samples	Concentration (ppb) Range	Mean	Reference
Urban:					
Southington, CT	1980	2	23,000–120,000[a]		Hall 1984
National Priorities List:					
Lang property, NJ	1985	NS	ND–980[b]	322	EPA 1987c
surface	1984	NS	ND–140	71	EPA 1987b
subsurface		NS	13,000[c]		
Gallaway Ponds site, TN					
1,1,1-Trichloroethane producer/user:					
Plant A	1976–1977	4	0.06–0.68		Battelle Labs 1977
Plant B		2	0.45–0.94		
Plant C		2	0.13–0.28		
Plant D		2	0.14–1.0		
User A		2	0.40–0.65		
Summit National, OH (NPL site)	1987				EPA 1988a
on-site surface		31	3[d]–51,000[b]	2,216[b]	
on–site subsurface (2–4 feet)		5	10–43,000[b]	8,391[b]	
on-site subsurface (4–6 feet)		2	5–2,800[d,b]	561[b]	
on-site subsurface (6–8 feet)		15	4[d]–230,000[b]	10,252[b]	
Residence near a landfill:					
Stanislaus County, CA	September 1987	NS	1.4–11	4.9	Hodgson et al. 1992
	October 1987		2.8–9.4	6.1	

[a]Data reported in µg/L; converted to ppb using the conversion factor 1 ppb = 1 µg/L
[b]Data reported in µg/kg; converted to ppb using the conversion factor 1 ppb = 1 µg/kg
[c]Data reported in ppm; converted to ppb using the conversion factor 1 ppb = 0.001 ppm
[d]Data were estimated.

ND = not detected; NS = not specified

TABLE 5-6. Detection of 1,1,1-Trichloroethane in Foods

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Unprepared, uncooked, off-the-shelf	Split peas	NS		3	Daft 1987
	Allspice			16,000	
	Pickling spice			549	
	Celery seed			909	
	Tea			10	
	Dumplings (dry)			7	
	Instant hot cereal			421	
	Ready-to-eat cereals			4	
	Cake mix (golden)			8	
	Cake mix (yellow)			87	
	Pancake mix			16	
	Breaded fish			2	
	Onion rings (precooked)			76	
Intermediate	Yellow corn meal	1984		3.8	Heikes and Hopper 1986
	Fudge brownie mix		2.9–3.0	0.74	
	Yellow cake mix				
Fresh	Nectarine	1985–1986		NS[a]	Takeoka et al. 1988
Cooked, aroma	Beef	NS		NS[a]	Galt and MacLeod 1984
Prepared	Bakers cheese	NS		1.3[b]	Uhler and Diachenko 1987
	Cottage cheese	NS	2.7–10.6	6.4	Miller and Uhler 1988
	Ricotta cheese		ND–30.6	3.0	
	Mozzarella (skim milk)		9.5–37.3	1.2	
	Vanilla ice cream		NS–7,500		
	Chocolate ice cream				
	Butter pecan ice cream				
	Butter				
Cooked, aroma	Baked potatoes	NS		ND	Coleman et al. 1981
Ice	Commercial machine	1975 (NS)		0.0039[c]	Su and Goldberg 1976

TABLE 5-6. Detection of 1,1,1-Trichloroethane in Foods (continued)

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Cereals	Shredded wheat	NS		4[b]	Daft 1988
	Raisin bran			6	
	Granola, plain			22	
	Oat ring			6	
	Rolled oats, cooked			35	
	Farina, cooked			8	
	Corn grits, cooked			3	
Vegetables	Peas, cooked	NS		1[b]	Daft 1988
	Peas, canned			2	
	Corn, boiled			2	
	Onion rings, cooked			9	
	French fries, cooked			2	
	Mashed potatoes			6	
	Sweet potatoes, candied			3	
	Cream of potato soup			2	
	Catsup			2	
Baked goods	Cornbread	NS		3[b]	Daft 1988
	Bisquits, baking powder			2	
	Blueberry muffins			11	
	Saltine crackers			7	
	Corn chips			9	
	Pancakes			3	
	Potato chips			8	
	Macaroni and cheese			2	
	Chocolate cake/icing			40	
	Yellow cake			40	
	Coffeecake, frozen			14	
	Donuts, cake, plain			17	
	Sweet roll, Danish			29	
	Cookies, chocolate chip			8	
	Cookies, sandwich			28	
	Apple pie, frozen			14	

TABLE 5-6. Detection of 1,1,1-Trichloroethane in Foods (continued)

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Nuts/nut products	Peanut butter, creamy	NS		10[b]	Daft 1988
	Peanuts, dry roasted			24	
	Pecans			228	
Dairy products	Whole milk	NS		1[b]	Daft 1988
	Chocolate milk			5	
	Milkshake, chocolate			152	
	Yogurt, strawberry			2	
	Cheese, processed			8	
	Cheese, cheddar			16	
	White sauce			10	
	Margarine, stick			13	
	Butter, stick			18	
	Cream, half & half			4	
	Ice cream, chocolate			4	
	Instant pudding, chocolate			1	
	Ice cream sandwich			15	
	Ice milk, vanilla			520	
Sugars, jams, candy	Candy, milk chocolate	NS		15[b]	Daft 1988
Meats, meat dishes	Beef, ground, fried	NS		8[b]	Daft 1988
	Beef, chuck roast			6	
	Beef, sirloin, cooked			10	
	Pork, ham, cured			5	
	Pork chop, cooked			76	
	Pork, sausage, cooked			7	
	Pork, bacon, cooked			2	
	Pork roast, loin, cooked			3	
	Lamb chop, cooked			7	
	Veal cutlet, cooked			8	
	Chicken, pieced, fried			14	
	Frankfurters, cooked			33	
	Bologna				

TABLE 5-6. Detection of 1,1,1-Trichloroethane in Foods (continued)

Type	Food	Sampling dates	Concentration (ppb) Range	Mean	Reference
Meats, meat dishes (continued)	Salami	NS		8	Daft 1988
	Tuna, canned in oil			3	
	Shrimp, breaded, fried			3	
	Fish sticks, cooked			12	
	Pizza, cheese, cooked			8	
	One-fourth pound			27	
	hamburger			15	
	Meatloaf, beef			4	
	Chicken noodle casserole			2	
	Lasagna			6	
	Potpie, chicken			10	
	Frozen dinner, chicken			2	
	Brown gravy				
Infant/toddler blends	Oatmeal, applesauce, banana	NS		6[b]	Daft 1988
Fruits	Apple, red, raw	NS		3[b]	Daft 1988
	Grapes, purple/green			2	
	Raisins, dried			16	
	Prunes, dried			21	
	Avocado, raw			32	
	Grapefruit juice			4	
	Lemonade			11	
Clear beverages	Grape juice	NS		3[b]	Daft 1988
	Whiskey, 80 proof			2	

[a]Detected in sample; no quantitative results given
[b]Data reported in ng/g; converted to ppb using the conversion factor 1 ppb = 1 ng/g
[c]Data reported in pg/mL; converted to ppb using the conversion factor 1 ppb = 1,000 pg/mL

ND = not detected; NS = not specified

1,1,1-Trichloroethane has been detected in four shoe and leather glues in Denmark in the concentration range 0.1-2.7% (wt/wt) (Rastogi 1992). Six samples of glues manufactured in the United States and in Europe and used for assembling various consumer goods and toys contained 1,1,1-trichloroethane in the concentration range 0.002-97.5% (wt/wt) (Rastogi 1993). In various brands of imported typing correction fluids in Singapore, the equilibrium vapor phase concentration of 1,1,1-trichloroethane ranged from <1 to 95% (v/v) (Ong et al. 1993).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The ubiquitous occurrence of low levels of 1,1,1-trichloroethane in ambient air and other environmental samples, together with the fact that many consumer products contain this chemical, suggests that much of the general population of the United States is exposed to low levels of 1,1,1-trichloroethane. This exposure can occur occupationally, environmentally, or as a result of the use of commercial products that contain 1,1,1-trichloroethane. 1,1,1-Trichloroethane has been detected in the blood, milk, breath, and urine of humans. Data on human body burdens associated with this compound can be found in Table 5-7. Table 4-2 provides a sampling of consumer products containing 1,1,1-trichloroethane. The levels of this chemical in human breath have been correlated with its levels in personal air by probability-based population studies (Wallace et al. 1985, 1986c, 1987a, 1988). If the average urban concentration of 1,1,1-trichloroethane is taken to be 1 ppb and the average rural concentration is taken to be 0.1 ppb, then daily nonoccupational intakes of 108 and 10.8 ug/day, respectively, can be obtained based on an average human air intake of 20 m^3/day. In areas where 1,000 ppb have been measured, the daily intake using this methodology would be 108 mg. However, Wallace et al. (1984a) have determined that the mean daily air exposure for 12 subjects from urban New Jersey and Research Triangle Park, North Carolina, was 370 mg. Further, the mean daily intake from all sources (air, food, and water) was between 50 and 1,000 mg/day for 1,1,1-trichloroethane (Wallace et al. 1984a).

1,1,1-Trichloroethane has been detected in newly constructed buildings (Wallace et al. 1987b). In a recent “shopping basket” survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products preselected to contain solvents at concentrations >0.l% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in all 67 categories of household products (1,026 brands tested) likely to be in the average U.S. home (Frankenberry et al. 1987; Maklan et al. 1987). The

TABLE 5-7. Detection of 1,1,1-Trichloroethane in Human Samples

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Adipose tissue:					
USA	1984	46	ND–830[a]	48	Stanley 1986a, 1986b
Blood/serum:					
New Orleans, LA		250	ND–26	NS	Antoine et al. 1986
Old Love Canal, NY	1978	9	0.24–1.8[b]		Barkley et al. 1980
Denver, CO	1976	3	1,300–2,700[c]	1,800	Gunter et al. 1977
Milk					Pellizzari et al. 1982
Bridgeville, PA; Bayonne, NJ; Jersey City, NJ; Baton Rouge, LA		12	NS		
Breath:					
Chicago, IL		387		0.0018[d]	Krotosznski et al. 1979
Texas		10	ND–140 (µg/hr)	40	Conkle et al. 1975
Old Love Canal, NY	1978	9	Trace–0.513[e]		Barkley et al. 1980
Chapel Hill, NC	1978	17	1.1–8.72[f]	81.81	Zweidinger et al. 1983
Beaumont, TX		17	0.081–29.6	15.97	
New Jersey					
fall	1981	322		1.2[f]	Wallace et al. 1987a
summer	1982	110		0.95	
winter	1983	49		0.37	
Devils Lake, ND		23		1.7	
Bayonne/Elizabeth, NJ	1980	48(9)	0.022–16.0[f]	0.88	Wallace et al. 1984a
	1981	295–339	ND–95	0.88[g]	Wallace et al. 1985
		17(3)	0.053–1.4	0.11	
Research Triangle Park, NC					
Los Angeles, CA					
winter	1984	112–115		1.17[g,f]	Wallace et al. 1987d
spring		51		0.70	

TABLE 5-7. Detection of 1,1,1-Trichloroethane in Human Samples (continued)

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Antioch-Pittsburgh, PA		66–69		0.017	
Elizabeth-Bayonne, NJ	1981	295–339	NS–96.2	2.78	Wallace et al. 1984b, 1985, 1986b, 1987a
Elizabeth-Bayonne, NJ	1981	48	0.022–15.7		Wallace et al. 1984a
Research Triangle Park, NC	1981	17	0.054–1.142		
Urine:					
Old Love Canal, NY	1978	9	0.03–0.180	100	Barkley et al. 1980

[a] Data in ng/g; 1 ppb = 1 ng/g
[b] Data in ng/mL; 1 ppb = 1 ng/mL
[c] Data in mg/dL; 1 ppb = 0.00001 mg/dL
[d] Data in ng/L; 1 ppb = 1000 ng/L
[e] Data in ng/m^3; 1 ppb = 5400 ng/m^3
[f] Data in $\mu g/m^3$; 1 ppb = 5.4 $\mu g/m^3$
[g] Weighted geometric mean

ND = not detected; NS = not specified

categories of these common household products are given in Table 4-2. The occurrence of 1,1,1-trichloroethane in 62% of the effluent samples taken from a community septic tank also suggests the presence of this compound in household products (De Walle et al. 1985).

Human exposure could occur directly via ingestion of contaminated water, but also indirectly through the inhalation of 1,1,1-trichloroethane that has volatilized from contaminated tap water. Based on a theoretical concentration of 1 mg/L (ppm) of 1,1,1-trichloroethane in tap water, the average estimated air concentrations for the entire house, bathroom, and shower stall were $2.3x10^{-4}$, $5.1x10^{-3}$, and $2.6x10^{-2}$ mg/L, respectively (McKone 1987). For a tap water concentration of 20 mg/L, the estimated daily exposure to 1,1,1-trichloroethane was 20.0 mg from ingestion, and 22.8 mg from inhalation while showering (Foster and Chrostowski 1986). The Total Exposure Assessment Methodology (TEAM) studies demonstrated that levels of personal air exposure determined using samples obtained on the same day could vary by orders of magnitude for subjects living in the same municipality, most likely as a result of variances in consumer practices and occupation (Hartwell et al. 1987a, 1987b, 1992; Wallace 1986, 1987; Wallace et al. 1986a, 1986b, 1988, 1989; Zweidinger et al. 1983). The maximum exposure levels of 1,1,1-trichloroethane during personal activities were: 185 ppb when visiting the dry cleaners, 18.5 ppb when working in a chemistry lab, 12 ppb when working as a lab technician, 48 ppb when using household cleaners, 20 ppb when using pesticides, and 20 ppb when using paint (Wallace et al. 1989). Exposure of the general population from the use of commercial products may be more significant than exposure resulting from industrial release.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, it has been statistically estimated that ≈2,528,300 workers in the United States were potentially exposed to 1,1,1-trichloroethane (NIOSH 1990). The largest number of workers are exposed in the following types of industries/services: sewing machine operators in apparel industry; registered nurses, maids, janitors and cleaners in hospitals; electricians, technicians, assemblers, installers, machinists and repairers in electrical and electronic industry; and janitors and cleaners in building maintenance service. From the existing monitoring data, it appears that most occupational exposure occurs by inhalation.

Specific industrial applications of 1,1,1-trichloroethane that might result in elevated levels of exposure are processes involving the degreasing and cleaning of fabricated metal parts (Gunter et al. 1977; Kominsky 1976; Levy and Meyer 1977; Markel 1977), manufacture of electronic components (Giles

and Philbin 1976), mixing and application of commercial resins (Giles 1976), and spray painting and spray gluing (Whitehead et al. 1984). Table 5-8 lists occupations in which 1,1,1-trichloroethane has been detected in the air. Other occupations where workers can be exposed to 1,1,1-trichloroethane include automotive assembly plants (Nelson et al. 1993), kraft pulp mills (Rosenberg et al. 1991) and fuel cell assembly plants (NIOSH 1993). In a recent survey (1990-1991) of a fuel cell assembly plant, the levels of 1,1,1-trichloroethane in some of the personal breathing zone and general area samples were found to exceed the NIOSH short-term exposure limit of 350 ppm (NIOSH 1993).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The general population is potentially exposed to low levels of 1,1,1-trichloroethane through the ingestion of contaminated water or food. Low levels of contamination in drinking water sources have been documented (Althoff et al. 1981; Barkley et al. 1980; Burmaster 1982; EPA 1986a; Krill and Sonzogni 1986; Wallace et al. 1984a; Zaki 1986). According to Table 5-2, 0.01-12,220 ppb 1,1,1-trichloroethane have been found in drinking water sources. 1,1,1-trichloroethane is used as a component of adhesives for food packaging, and this practice may contribute to human exposure by ingestion (Miller and Uhler 1988). Airtight, highly-insulated houses are likely to have high indoor concentrations from use of household products containing 1,1,1-trichloroethane. Very high levels of exposure are expected to occur for those who intentionally inhale 1,1,1-trichloroethane for its euphoric/narcotic properties.

Workers involved in processes using this compound may encounter high exposure levels. Occupations in which 1,1,1-trichloroethane has been found in the air are given in Table 5-8. Analysis of these data shows that ambient air concentrations in industries using 1,1,1-trichloroethane are up to four orders of magnitude higher than what is typically found in urban air.

1,1,1-Trichloroethane is used in some adhesive remover pads of incubators in intensive care nurseries, and there is evidence that infants in incubators can be exposed to high concentrations of 1,1,1-trichloroethane (Gallagher and Kurt 1990).

TABLE 5-8. Occupational Air Levels of 1,1,1-Trichloroethane

Location/occupation	Sampling dates	Concentration		Reference
		Range	Mean	
Bozeman, MT	1976			Taketomo and Grimsrud 1978
Auto repair garage			2.2	
Bookstore			6.7	
Restaurant			0.2	
Department store		0.8–1.7		
Newspaper press room			2.2	
Grocery store		1.9–21		
Dry cleaner		1.8–14.4		
Chemistry building (academic)		0.1–1.2		
Tampa, FL				
Telephone central office	1979	27–65		Oblas et al. 1979, 1980
Hobbs, NM				
Telephone business office			50	
Waltham, MA				
Laboratory air			4.5	
Organic solvent recycling plant	1984	ND–20,000[a]	3,110	Kupferschmid and Perkins 1986
Booth spray painting/gluing	1981	NS–22,000[a]	1,200	Whitehead et al. 1984
Screw machine manufacturing company, AR	1976	12,000–99,800[b]		Markel 1977
Rifle scope producer, Denver, CO	1976	7,700–478,000[b]		Gunter et al. 1977
Heating and cooling coil manufacturing, IL	1976	1,460–16,600[b]		Levy and Meyer 1977
Electric apparatus manufacturing, PA	1975	2,500–79,500[a]		Giles 1976
Electrical resistor manufacturing, PA	1976	6,000–83,000[a]		Giles and Philbin 1976
Valve part manufacturer, IN	1976	4,000–37,000[a]		Kominsky 1976
Aircraft manufacturer, GA	1983–1984	ND–23,000[a]		Salisbury et al. 1986
Sport racket manufacturer, CO	1985	NS		Pryor 1987
Nail manufacturer, CO	1987	7,510–406,000[b]		NIOSH 1987
Fiber manufacturer, IL	1986	59–115[b]		Daniels et al. 1988
Mens' shirt company, IN	1974			Nord 1974
Film optical shops, NY	1979	500–1,320,000[b]		Peter and Edelbrock 1980
Joint/shaft manufacturer, IN	1979	800–1,300[a]		McQuilkin et al. 1979

TABLE 5-8. Occupational Air Levels of 1,1,1-Trichloroethane (continued)

Location/occupation	Sampling dates	Concentration		Reference
		Range	Mean	
Battery manufacturer, CO	1979	9,160–36,400[b]		NIOSH 1980a
Typesetter/photographer, GA	1979	3,900–4,600[a]		NIOSH 1980b
Graphic services, OH	1979	<1,000[a]		NIOSH 1980c
Welding shop	1979	3,200–4,799[a]		Vegella 1979
Suitcase manufacturer, CO	1978	500–756,000[a]		Apol and Singal 1979
Ski/tennis racquet manufacturing, CO	1979	22,500–85,800[b]		Gunter 1979
Sewer workers, OH	1981	1,000–40,000[a]		McGlothlin and Cone 1983
Solar cell producer, CA	1979	ND–74,000[b]		Briggs and Garrison 1982
Medical therapeutic system manufacturing, CO	1979	400–3,600[a]		NIOSH 1980d
Navigation information products, CO	1981	549–2,750[b]		Gunter 1983
Tractor manufucturer, ND	1979	ND–62,600[a]		NIOSH 1980e
U.S. Department of the Treasury, DC	1982	NS		Lee 1984
School district print shop, OR	1983	100[a]		Apol and Helgerson 1983
Electrical maintenance company, OH	1981	123,000–385,000[b]		Kominsky and Lipscomb 1985
Electrical commutators manufacturers, IL	1983	ND–4[a]		Almaguer 1985
Crystal fabricator, CO	1984	366–2700[b]		Gunter and Thoburn 1986
Silk screening of textiles, KS	1975	ND–75,000[b]		Hervin 1975
Aluminum vane manufacturers, OH	1976	74,000–396,000[a]		Giles 1977
Catapult cylinder manufacturers, OH	1975	2,400–18,400[a]		Giles 1977
Chemical recovery plant, OH	1980	1,900–4,500[b]		Albrecht 1980
Pump manufacturer, NY	1978–1979	ND–2,930		Fannick 1980
Uranium company, WY	1980	ND–155,000[b]		Gunter 1980
Theater, NY	1985	458–10,700[b]		Fannick 1986

[a]Data reported in ppt; converted to ppb using the conversion factor 1 ppb = 1,000 ppt
[b]Data reported in mg/m^3; converted to ppb using the conversion factor 1 ppb = 0.0054 mg/m^3

ND = not detected; NS = not specified

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,1-trichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,1,1-trichloroethane are well documented, and little additional information in this area is required. Only one BCF for 1,1,1-trichloroethane was located in the available literature. This value is, however, consistent with what one would expect based on the other physical and chemical properties of 1,1,1-trichloroethane.

Production, Import/Export, Use, Release, and Disposal. Data on the production, use, release, and disposal of 1,1,1-trichloroethane in the United States are well represented in the literature. The volume of 1,1,1-trichloroethane produced in the United States is known. According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, future U.S. production will be cut incrementally until phase-out by January 1, 1996 (EPA 1993k). The large annual production of this compound and its presence in consumer products indicate that a large segment of the general population is potentially exposed to 1,1,1-trichloroethane. The use of 1,1,1-trichloroethane is well-documented. It is used extensively in industrial applications, and it is found in numerous consumer products for the home. Mandates on production, however, are expected to decrease the use of 1,1,1-trichloroethane and subsequent potential exposure to 1,1,1-trichloroethane.

There are a few food monitoring studies in the literature that provide several examples of food contamination with 1,1,1-trichloroethane. The ubiquitous nature of 1,1,1-trichloroethane suggests that additional information in this area would allow a complete determination of the levels of human exposure to this chlorinated solvent. The release of 1,1,1-trichloroethane to the environment is well established since there are numerous studies that indicate the presence of this compound in environmental media. The quantity of 1,1,1-trichloroethane released to the environment during its production, formulation, and use is known. 1,1,1-Trichloroethane is listed on the Toxics Release Inventory. Methods for the disposal of 1,1,1-trichloroethane exist. Data on the removal of 1,1,1-trichloroethane from waste streams during biological treatment processes are lacking. Information on the amount of l,l, 1-trichloroethane disposed of annually is scarce. Rules and regulations governing the disposal of 1,1,1-trichloroethane exist.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, became available in May of 1994. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Data on the environmental fate of 1,1,1-trichloroethane are well represented in the literature. The partitioning of 1,1,1-trichloroethane from soil or water to the atmosphere is well established, and there is sufficient evidence to indicate that the compound can leach into groundwater. The relatively slow rate of degradation and the major routes of 1,1,1-trichloroethane degradation in all environmental compartments have been established. The relatively long persistence of trichloroethane in the atmosphere indicates that a significant portion of this compound migrates to the stratosphere. Data on the biodegradation of 1,1,1-trichloroethane in soil are particularly lacking.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans .and animals have demonstrated the bioavailability of 1,1,1-trichloroethane from air and drinking water. Although some data on the bioavailability of 1,1,1-trichloroethane from air to mammalian skin (Mattie et al. 1994), and from air to other mammalian tissues (blood, muscle, liver) (Connell et al. 1993) are available, no studies on the bioavailability of 1,1,1-trichloroethane from food or soil were located. Some of the important routes of exposure to 1,1,1-trichloroetbane for residents near waste sites will be inhalation of airborne dusts, ingestion of soil (children) and dermal contact

with contaminated soil (mostly children). Therefore, it would be helpful to develop reliable data for the bioavailability of 1,1,1-trichloroethane from dust as a result of inhalation of contaminated airborne dust, from soil as a result of ingestion of soil, and from soil as a result of dermal contact with soil.

Food Chain Bioaccumulation. 1,1,1-Trichloroethane is not believed to bioconcentrate in fish and aquatic organisms; thus, it is not expected to biomagnify in the food chain. There are limited data regarding food chain biomagnification of 1,1,1-trichloroethane.

Exposure Levels in Environmental Media. Volumes of data exist on levels of 1,1,1-trichloroethane in environmental media, with the exception of levels in soil samples. Continued monitoring of environmental media is warranted. Blind monitoring at this stage, however, might be replaced with methods that allow both the continued determination of the environmental burden of 1,1,1-trichloroethane and correlation with human burden, like that performed in the TEAM studies. These and other studies have estimated human intake of 1,1,1-trichloroethane from environmental media. For members of the general population near hazardous waste sites, total exposure to 1,1,1-trichloroethane will include exposure from environmental media and exposure from consumer products.
Reliable monitoring data for the levels of 1,1,1-trichloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,1,1-trichloroethane in the environment can be used in combination with the body tissue/fluid levels of 1,1,1-trichloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. 1,1,1-Trichloroethane has been detected in human tissues and expired air. Studies have recently determined that the potential for exposure of the general population may be significantly higher inside the home. Additional information that correlates the lifestyle of the individual with the total body burden of 1,1,1-trichloroethane would aid in reducing future exposure to the general population. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for 1,1,1-trichloroethane were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is

made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

No studies were located regarding ongoing research concerning the environmental fate of 1,1,1-trichloroethane.

As part of the Third National Health and Nutrition Evaluation Survey, the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for 1,1,1-trichloroethane and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring 1,1,1-trichloroethane, its metabolites, and other biomarkers of exposure and effect to 1,1,1-trichloroethane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

In the analysis of 1,1,1-trichloroethane in biological materials, a key factor in the determination is the sample matrix under consideration. In the broadest sense, this can be broken down into liquid samples (e.g., blood or urine), solid samples (which would include adipose tissue, liver samples), and expired air samples. After 1,1,1-trichloroethane has been liberated from the sample matrix, a number of similar techniques can then be used to complete the analysis. A synopsis of these methods can be found in Table 6-l. In general, the methods for determining the metabolites of 1,1,1-trichloroethane are the same as those used for the parent compound, with slight modifications (Nolan et al. 1984).

The quantification of 1,1,1-trichloroethane in blood and urine samples can be achieved by the initial use of purge and trap methodology (Antoine et al. 1986; Barkley et al. 1980). This technique involves the liberation of the volatile chlorinated hydrocarbon by bubbling an inert gas through the sample matrices at elevated temperatures (≈50-95 ºC). Higher temperature increases the vapor pressure of the compound, and the bubbling action serves, essentially, to increase the gas-liquid partition, and thus volatilize the compound of interest. The gaseous sample is collected on an adsorption tube, which frequently uses a polymeric sorbent such as Tenax GC.

TABLE 6-1. Analytical Methods for Determining 1,1,1-Trichloroethane in Biological Samples

Sample matrix	Preparation method	Analytical method	Limit	Recovery	Reference
Exhaled air	Collection in Tedlar bag; adsorbtion on Tenax GC; thermal desorption	HRGC/MS	0.1 µg/m^3	87–94	Barkley et al. 1980; Wallace et al. 1984a, 1985, 1987a
Exhaled air	Collection in charcoal cloth wafers; desorption in carbon disulfide	GC/FID	2 mg/m^3 (for 50 L sample)	89–120	Glaser and Arnold 1989
Exhaled air	Collection into canister by portable spirometer; aliquot injection into a cryogenic trap	HRGC/MS	3.3 µg/m^3 (for 300 L sample)	94–98	Raymer et al. 1990
Urine	Purging at 50 °C; trapping on Tenax GC; thermal desorption into GC	HRGC/MS	No data	No data	Barkley et al. 1980
Adipose tissue	Purging at 95 °C; trapping on Tenax GC; thermally desorption at 250 °C	HRGC/MS	0.01 mg/kg	No data	Stanley 1986a,1986b
Blood	Purging at 50 °C; trapping on Tenax GC; thermal desorption	HRGC/MS	No data	No data	Antoine et al. 1986; Barkley et al. 1980
Blood	Purging at 30 °C; trapping on Tenax GC; thermal desorption into GC	HRGC/MS	0.049 µg/L	147	Ashley et al. 1992
Blood	Static headspace	HRGC/FID	<0.1 mg/L	214 (at 0.5 mg/L)	Dills et al. 1991
Liver, kidney, brain, heart, lung, perirenal fat and skeletal muscle	Homogenization with ice-cold saline and iso-octane; vortexing and centrifugation. Iso-octane layer withdrawn for head space analysis	GC/ECD	1 ng	85.5–91.3	Chen et al. 1993
Milk	Purging at 70 °C; trapping in Tenax GC; thermal desorption	HRGC/MS	No data	No data	Pellizzari et al. 1982

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry

At this point, the sample is analyzed by gas chromatography (GC), the analytical method of choice for volatile halogenated hydrocarbons. Information on the analysis of these samples by GC is presented in Section 6.2, with a discussion of the advantages and disadvantages of each method. The technique of Antoine et al. (1986) showed a 5% variance on a series of 2 ppb spiked samples, and the analysis had a linear response ranging from 0.5 to 50 ppb. Although infra-red spectrometry has less sensitivity than electron capture detectors (ECD), Hall electroconductivity detectors (HECD), and mass spectrometric detectors (MS), it has been used to quantify the levels of 1,1,1-trichloroethane in biological samples (IARC 1979).

The concentration of 1,1,1-trichloroethane in solid samples can be determined by headspace techniques, which involve analysis of the air above a heated sample in either a dynamic or a static system. In a static system, an aliquot of the atmosphere above the sample is obtained and analyzed by direct GC. In a dynamic system, an inert gas is passed over the top of a heated, rapidly stirred suspension of sample in water (Stanley 1986a, 1986b). The gas stream is then passed through an adsorption tube, trapping the volatile compounds. For adipose tissue, the detection limits were 0.01 mg/kg and the average recovery for spiked samples (concentration range 0.15-0.44 μg/20 g tissue) was 105%, with a precision of 11.8% (Stanley 1986a, 1986b).

In biological samples, losses during the sample preparation stage (weighing, transferring, etc.) can arise due to the volatility of 1,1,1-trichloroethane or from an incomplete recovery from the biological matrix. Samples should be analyzed shortly after they are obtained. Otherwise, they should be carefully stored at low temperature, preferably in a freezer. Handling and manipulation also should be kept to a minimum, preventing both premature loss by volatilization and contamination of the sample through the adsorption of vapors from ambient air. The need for blank water with very low levels of volatile organic compounds (VOCs) has increased because of the constant improvement in the sensitivity of detection of these VOCs. A method that uses distillation in conjunction with helium stripping has been described to obtain high purity blank water (Cardinali et al. 1994).

6.2 ENVIRONMENTAL SAMPLES

A short description of the methods used for analysis of 1,1,1-trichloroethane in environmental samples is presented in Table 6-2. An extensive list of methods for analysis of 1,1,1-trichloroethane in environmental samples can be compiled from the literature. Two methods are commonly used for

TABLE 6-2. Analytical Methods for Determining 1,1,1-Trichloroethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Charcoal tube collection and carbon disulfide desorption	GC/FID (NIOSH 1003)	18 ppm	No data	NIOSH 1987
Ambient air	Trapping on adsorbent; thermal desorption	HRGC/ECD	0.006 µg/m^3 (based on 127 L sample)	100	Frank and Frank 1988
Waste water	Purge and trap onto adsorbent; desorption into GC column by rapid heating	GC/HECD (EPA 601)	0.03 µg/L	75±12	EPA 1982c
Waste water	Purge and trap onto adsorbent; thermal desorption	GC/MS (EPA 624)	3.8 µg/L	102±16	EPA 1982a
Solid waste matrices, groundwater, liquid wastes, sediment	Purge and trap into adsorbent; thermal desorption	GC/MS (EPA-8240 SW 846)	5 µg/L (groundwater) 5 µg/kg (soil and sediment)	113 (at 10 µg/kg)	EPA 1986e
Soil	Purge and trap onto adsorbent; rapid heating desorption	GC/MS (EPA Contract Lab)	5 µg/kg	No data	EPA 1987a
Drinking water	Purge and trap onto adsorbent; backflush to cryogenically cooled trap	GC/HECD (EPA 502.1) HRGC/HECD (EPA 502.2)	0.003 µg/L 0.01 µg/L	93±8 96±2.6	EPA 1986a
Drinking water, raw source water	Purge and trap onto adsorbent; backflush to packed or cryogenically cooled capillary trap	GC/MS (EPA 524.1) HRGC/MS (EPA 524.2)	0.3 µg/L 0.04 µg/L	105±8.9 100±4	EPA 1988b, 1988c
Food	Heating sample in closed container at 95 °C for 55 minutes; analysis of headspace gas	GC/ECD	0.6–2.4 µg/kg (for various foods)	No data	Norman 1991

ECD = electron capture detector; EPA = Environmental Protection Agency; FID = flame ionization detector; GC = gas chromatography; HECD = Hall Electroconductivity detector; HRGC = high resolution gas chromatography; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health

collection of 1,1,1-trichloroethane and other volatile organics in ambient and occupational air. One method uses adsorbents to trap and concentrate organics in air, and the other method uses passive stainless steel canisters (SUMMA canisters). The advantage of SUMMA canisters is that sample breakthrough does not occur with this method as it may occur with adsorbent tubes (Hsu et al. 1991). The disadvantages of the canister method are its inability to concentrate pollutants during sample collection and the potential analytical problems associated with the presence of moisture in the sample (Bianchi and Vamey 1993). In all methods, however, there is a consensus that after the sample collection and preparation stage, mixture separation and quantitative analysis is best done with GC, coupled with an assortment of detectors. Standardized methods, with slight alterations, also can be used for determining the metabolites of 1,1,1-trichloroethane (Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987).

The analysis of 1,1,1-trichloroethane in occupational air samples can be accomplished by NIOSH method 1003 (NIOSH 1987). The sample is obtained in the field with a pumping system to pass a measurable quantity of air (≈3 L) through a tube loaded with a solid sorbent, such as charcoal. Extraction of the tube with the solvent CS_2 liberates the 1,1,1-trichloroethane collected, an internal standard is added, and quantitation is then achieved by GC. For packed column analysis, an OV-101 column using a flame ionization detector (FID) is given as the preferred choice (alternates, including capillary columns, are acceptable). For the estimation of low levels of 1,1,1-trichloroethane in ambient air, thermal desorption following collection of the sample in an absorbent trap is the method of choice (Frank and Frank 1988).

Capillary columns are used to separate 1,1,1-trichloroethane from the other components in a mixture. Capillary columns provide wider versatility offering superior resolution of components. A comparison of capillary and packed column for analysis of volatile organics by GC is available (Clark and Zalikowski 1990). Narrow-bore capillary columns have high resolving power but may not be suitable for headspace analysis because of easy column saturation (Ohno and Aoyama 1991). Wide-bore capillary columns are suitable in such cases (Ohno and Aoyama 1991). Different detectors can be used; ECD, HECD, and MS have been described. The MS is the most selective detector, but the HECD is the most sensitive. Both closed path and open path Fourier transform infrared spectrometry (FTIR) have recently been used for the determination of 1,1,1-trichloroethane in air (Carter et al. 1992; Trocha and Samimi 1993; Xiao and Levine 1993). Although the FTIR methods have higher detection

limits than some of the other conventional methods, they afford the opportunity of remote monitoring of real-time samples (Xiao and Levine 1993).

In the analysis of 1,1,1-trichloroethane in air, the weakest link in analysis is irreversible adsorption of the desired compound to the sorbent material during sample collection For highly volatile, nonpolar compounds such as 1,1,1-trichloroethane, complete removal of the substrate may not occur if the adsorbent irreversibly adsorbs the substrate.

The collection methods commonly used for water and aqueous effluents are grab or proportional sampling. However, a solid phase microextraction method which involves exposing a fused silica fiber coated with a stationary phase to the aqueous sample until equilibrium is achieved, has been proposed as a collection method (Arthur et al. 1992). Analysis for 1,1,1-trichloroethane in municipal and industrial waste water is described in EPA method 601-purgeable halocarbons (EPA 1982a). A 5 mL grab sample is connected to an apparatus called a purging chamber. This chamber allows for an inert gas to be sparged through the water sample, carrying the 1,1,1-trichloroethane onto an adsorbent tube. The organics are subsequently desorbed from the adsorbent tube by rapid heating and back flushing into the GC column. Analysis is then made by GC elution using an HECD. Detection limits for this method are given as 0.03 μg/L, with a 75% average recovery for spiked samples. EPA test method 624, purgeables, also can be used for the analysis of 1,1,1-trichIoroethane in waste water (EPA 1982a). This method is similar to method 601, except that MS is used for quantitation.

EPA method 502.1 can be used in the analysis of 1,1,1-trichloroethane in finished or raw source water (EPA 1986a). This method is analogous to method 601. The detection limit for this method is 0.003 ug/L, with an average recovery of 93%.

The EPA guidelines for contract laboratories (EPA 1986c) include methodology for the analysis of groundwater and soil samples. The method for water analysis is similar to method 524.1. Detection limits for this method are given at 5 μg/kg.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether

adequate information on the health effects of 1,1,1-trichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The urinary concentration of 1,1,1-trichloroethane can be used as an appropriate biological indicator of exposure (Imbriani et al. 1988; Salkinoja-Salonen and Jokela 1991). Both in the experimentally exposed subjects and in the occupationally exposed workers, the urinary concentration of 1,1,1-trichloroethane showed a linear relationship to the corresponding environmental time-weighted average concentration with a correlation coefficient of 0.90495 (Imbriani et al. 1988). Analytical methods of sufficient sensitivity are available to determine 1,1,1-trichloroethane in urine (Imbriani et al. 1988; Salkinoja-Salonen and Jokela 1991). There is no known effect of 1,1,1-trichloroethane that can be quantitatively related to its exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methodology for determining the levels of 1,1,1-trichloroethane and its biotic/abiotic degradation products such as 1,1-dichloroethene, 1,1-dichloroethane, and chloroethane in environmental samples are well established (Hallen et al. 1986; Mehran et al. 1988a; Parsons et al. 1985; Vogel and McCarty 1987). Existing methods that provide acceptable detection limits for background levels in the environment and for levels at which health effects occur can be found for all types of environmental samples. The precision, accuracy, reliability, and specificity of each method are well documented, and potential pitfalls have been described. Development of a new methodology to determine 1,1,1-trichloroethane in environmental samples that would provide both

increased speed and decreased levels of difficulty may be desirable in situations where environmental monitoring of 1,1,1-trichloroethane is required on a rapid or routine basis.

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of 1,1,1-trichloroethane and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion (ppt) range.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding 1,1,1-trichloroethane in air, water, and other media are summarized in Table 7-l.

ATSDR has derived an MRL of 2 ppm for acute inhalation exposure (14 days or less) to 1,1,1-trichloroethane, based on a LOAEL of 175 ppm for reduced performance of psychomotor tests in human volunteers in a study by Mackay et al. (1987).

ATSDR has derived an intermediate inhalation MRL of 0.7 ppm for 1,1,1-trichloroethane based on a study by Rosengren et al. (1985) which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months.

Neither a reference dose nor a reference concentration for 1,1,1-trichloroethane are available at this time.

1,1,1-Trichloroethane is on the list of chemicals appearing in “The Emergency Planning and Community Right-to-Know Act of 1986” (EPCRA) (EPA 19881). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to 1,1,1-trichloroethane to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an &hour time-weighted average (TWA) of 350 ppm. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1989).

1,1,1-Trichloroethane is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Sections 400-475, of the Code of Federal Regulations. 1,1,1-Trichloroethane is regulated as a group of chemicals controlled as Total Toxic Organics, and has specific effluent limitations, The point

source categories for which 1,1,1-trichloroethane is controlled as a Total Toxic Organic include electroplating and metal finishing (EPA 1981e, 1983c). The point source category for which 1,1,1-trichloroethane has specific effluent limitations is organic chemicals, plastics, and synthetic fibers (EPA 1987f, 19878).

According to the 1990 Clean Air Act Amendments and the Montreal Protocol, U.S. production of 1,1,1-trichloroethane will be cut incrementally until the proposed phase out occurs by January 1996 (EPA 1993n).

Under the Resource Conservation and Recovery Act (RCRA), 1,1,1-trichloroethane is as a hazardous waste in three categories: (1) wastes from non-specific sources; (2) wastes from specific sources; and (3) discarded commercial chemical products, off-specification species, container residues, and spill residues thereof (EPA 1980c, 1981a, 1981b).

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 3[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
EPA	Listed as hazardous air pollutant (HAP)	Yes	U.S. Congress 1990
OSHA	PEL TWA	350 ppm (1,900 mg/m^3)	29 CFR 1910.1000 (54 FR 2923) OSHA 1989
EPA OAR	Definition of Volatile Organic Compound (VOC)	Yes	40 CFR 51.100 EPA 1986f
	Subpart X - EPA Approval of MI's SIP: Coating Exclusion	Yes	40 CFR 52.1170 EPA 1972a
	Subpart RR - EPA Approval of TN's SIP: Definition of VOC	Yes	40 CFR 52.2222 EPA 1980d
	Subpart YY - EPA Approval of WI's SIP: Partial Exemption from VOC Control Requirements	Yes	40 CFR 52.2570 EPA 1972b
	Approval and Promulgation of Implementation Plan; WI (Proposed)	Yes	40 CFR 52 (59 FR 9158) EPA 1994a
	Approval and Promulgation of Implementation Plans: Revision to NJ SIP (Proposed)	Yes	40 CFR 52 (58 FR 38326) EPA 1993a
	Designation as a HAP	Yes	40 CFR 61.01 (50 FR 24314) EPA 1985c
	NESHAP for Halogenated Solvent Cleaning (Proposed)	Yes	40 CFR 63 (58 FR 62566) EPA 1993b
	NESHAP for Pulp and Paper Production (Proposed)	Yes	40 CFR 63 (58 FR 66078) EPA 1993c
	HAPs: Regulations Governing Constructed, Reconstructed or Modified Major Sources (Proposed)	Yes	40 CFR 63 (59 FR 15504) EPA 1994b
	Protection of Stratospheric Ozone: Baseline Production Allowances	Yes	40 CFR 82.5 EPA 1988e
	Availability of Production Allowances in Addition to Baseline Production Allowances	Yes	40 CFR 82.9 EPA 1988f
	App. A - Class I Controlled Substances	O_3 depletion wt. = 0.1	40 CFR 82 EPA 1991f
	App. F - Listing of Ozone Depleting Chemicals	Yes	40 CFR 82 EPA 1993d

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Labelling of Products Using Ozone Depleting Chemicals: Definitions	Yes	40 CFR 82.104 EPA 1993e
	Warning Statement Requirement	Yes	40 CFR 82.106 EPA 1993f
	Form of Label Bearing Warning Statement	Yes	40 CFR 82.110 EPA 1993g
	Labelling Supplemental Proposal (Proposed)	Yes	40 CFR 82 (58 FR 69568) EPA 1993h
	Certification, Recordkeeping, and Notice Requirements	Yes	40 CFR 82.122 EPA 1993i
b. Water EPA OGWDW	MCL in drinking water	0.2 mg/L	EPA 1994c
EPA OW	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978a
	App. D - NPDES Permit Application Testing Requirement	Yes	40 CFR 122 EPA 1978b
	NPDES, Form 2D	Yes	40 CFR 122 EPA 1983a
	NPDES Instruction Form 2c	Yes	40 CFR 125 EPA 1979a
	Method 624 - Purgeables	Yes	40 CFR 136 EPA 1979b
	Method 1624 - Volatile Organic Compounds by Isotope Dilution GC/MS	Yes	40 CFR 136 EPA 1979c
	National Primary and Secondary Drinking Water Regulations: Analytical Methods - Organic Chemicals (Proposed)	Yes	40 CFR 141 (58 FR 65622) EPA 1993j
	App. C - Analysis of Trichloromethanes	Yes	40 CFR 141 EPA 1979d
	Registration Policies and Interpretations: Substances Determined to be Chemically Inert	Yes	40 CFR 153.139 EPA 1988g
	Tolerances and Exemptions from Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities: Exemptions from Tolerances	Yes	40 CFR 180.1001 EPA 1971a
	1,1,1,-Trichloroethane - Exemption from the Requirement of a Tolerance	Yes	40 CFR 180.1012 EPA 1971b
	Effluent Guidelines and Standards: Electroplating - Definition of Total Toxic Organic	>0.01 mg/L	40 CFR 413.02 EPA 1981c
	Organic Chemicals, Plastics, and Synthetic Fibers - Description of Bulk Organic Chemicals Subcategory	Yes	40 CFR 414.70 EPA 1992g

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Organic Chemicals, Plastics, and Synthetic Fibers - Toxic Pollutant Effluent Limitation and Standards for Direct Discharge Point Sources That Do Not Use End of Pipe Biological Treatment	Yes	40 CFR 414.91 EPA 1987g
	- maximum for any one day	54 µg/L	
	- maximum for monthly avg.	21 µg/L	
	Organic Chemicals, Plastics, and Synthetic Fibers - Toxic Pollutant Effluent Limitation and Standards for Direct Discharge Point Sources That Do Not Use End-of-Pipe Biological Treatment		40 CFR 414.101 EPA 1987h
	- maximum for any one day	59 µg/L	
	- maximum for monthly avg.	22 µg/L	
	Effluent Guidelines and Standards - Metal Finishing - Definition of Total Toxic Organic	>0.01 mg/L	40 CFR 433.11 EPA 1983b
	App. A - 126 Priority Pollutants	Yes	40 CFR 423 EPA 1982b
c. Food			
EPA	Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities:	Yes	HSDB 1994
	No tolerances for residue listed Exempted when used in the post-harvest fumigation of citrus fruits		
d. Other:			
EPA OERR	Reportable quantity	1,000 pounds	40 CFR 302.4 EPA 1988h
EPA OPP	Intent to Cancel, Restrict or Require Reregistration of Pesticide Products Containing 1,1,1-Trichlorethane (methyl chloroform)	No[b]	EPA 1993m
EPA OPTS	Specific Toxic Chemical Listings - Chemicals and Chemical Categories to Which this Subpart Applies	Yes	40 CFR 372.65 EPA 1988i
	Procedures Governing Testing Consent Agreement and Test Rules: Submission of Information	Yes	40 CFR 790.5 EPA 1985d
	Identification of Specif Chemical Substance and Mixture Testing Requirements: Submission of Information	Yes	40 CFR 799.5 EPA 1988j
	Identifition of Specific Chemical Substance and Mixture Testing Requirements: 1,1,1-Trichloroethane	Yes	40 CFR 799.4400 EPA 1984b
EPA OSW	App. I - Criteria for Classification of Solid Waste Disposal Facilities and Practices: Maximum Contaminant Levels	Yes	40 CFR 257 EPA 1979e

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	App. I - Criteria for Municipal Solid Waste Landfills: Constituents for Detection Monitoring	Yes	40 CFR 258 EPA 1991g
	Definition of Hazardous Waste	Yes	40 CFR 261.3 EPA 1992h
	Hazardous Waste from Non-specific Sources (F001, F002, F024, F025)	Yes	40 CFR 261.31 EPA 1981a
	Hazardous Waste from Specific Sources (K019, K020, K028, K029, K096)	Yes	40 CFR 261.32 EPA 1981b
	Listed Hazardous Waste (U226)	Yes	40 CFR 261.33 EPA 1980c
	App. VII - Basis for Listing Hazardous Waste	Yes	40 CFR 261 EPA 1981d
	App. VIII - Hazardous Constituents	Yes	40 CFR 261 EPA 1980d
	App. IX - Wastes Excluded from Non-specific Sources	Yes	40 CFR 261 EPA 1984a
	App. IX - Groundwater Monitoring List	Yes	40 CFR 264 EPA 1987i
	App. VIII - Potential PICs for Determination of Exclusion of Waste-Derived Residues	Yes	40 CFR 266 EPA 1991h
	LDR - Wastes to be Evaluated by August 8, 1988	Yes	40 CFR 268.10 EPA 1986g
	Constituent Concentrations in Wastes		40 CFR 268.43
	F001 - F005	0.054 mg/L (ww) 5.6 mg/L (nonww)	EPA 1988k
	F039	0.054 mg/L (ww) 5.6 mg/L (nonww)	
	K018, K019, K028, K029	0.054 mg/L (ww.) 6.0 mg/L (nonww)	
	K073	0.054 mg/L (ww) 6.2 mg/L (nonww)	
	U226	5.6 mg/L (nonww)	
Guidelines:			
a. Air:			
ACGIH	TLV TWA	350 ppm (1,910 mg/m^3)	ACGIH 1992
	STEL	450 ppm (2,460 mg/m^3)	
	BEI (in end-exhaled air)	40 ppm	
NIOSH	Ceiling (REL)	350 ppm (1,910 mg/m^3)	HSDB 1992
b. Water:			
EPA ODW	MCLG (final)	0.2 mg/L	EPA 1994c
	Health Advisories:		
	1-day	100 mg/L	EPA 1994c
	10-day	40 mg/L	
	Longer-term (child)	40 mg/L	
	Longer term (adult)	100 mg/L	
	Lifetime	0.2 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA OWRS	Ambient Water Quality Criteria for Protection of Human Health:		IRIS 1994
	Ingesting water and organisms:	1.84×10^4 µg/L	
	Ingesting organisms only:	1.03 µg/L	
NAS	SNARL	490 mg/L (24 hour)	NAS/NRC 1980
c. Other			
EPA	Carcinogen classification	Group D[c]	IRIS 1994
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient concentration guidelines or standards		NATICH 1992
AZ		2.00×10^4 µg/m^3 (1 hour)	
		1.10×10^3 µg/m^3 (24 hour)	
CT		3.80×10^4 µg/m^3 (8 hour)	
FL-Ftldle		3.80×10^1 mg/m^3 (8 hour)	
FL-Pinella		3.82×10^4 µg/m^3 (8 hour)	
		9.16×10^3 µg/m^3 (24 hour)	
IN		1.90×10^4 µg/m^3 (8 hour)	
IN-Innap		1.90×10^4 µg/m^3 (8 hour)	
LA		4.55×10^3 µg/m^3 (8 hour)	
MA		1.04×10^3 µg/m^3 (24 hour)	
		1.04×10^3 µg/m^3 (annual)	
ME		2.50×10^5 µg/m^3 (15 min.)	
		1.00×10^4 µg/m^3 (24 hour)	
		1.00×10^3 µg/m^3 (1 year)	
NC/Forco		1.20 mg/m^3 (24 hour)	
		2.45×10^2 mg/m^3 (15 min)	
ND		1.91×10^1 mg/m^3 (8 hour)	
		2.46×10^1 mg/m^3 (1 hour)	
NV		4.52×10^1 mg/m^3 (8 hour)	
NY		3.80×10^4 µg/m^3 (1 year)	
OK		1.91×10^5 µg/m^3 (24 hour)	
SD		3.80×10^4 µg/m^3 (8 hour)	
TX		1.91×10^4 µg/m^3 (30 min)	
VA		1.91×10^3 µg/m^3 (annual)	
VT		3.20×10^4 µg/m^3 (24 hour)	
WA-SWEST		1.90×10^5 µg/m^3 (8 hour)	
		6.33×10^3 µg/m^3 (24 hour)	
b. Water:			
	Water Quality Criteria: Human		CELDs 1994
AL	Water and fish consumption	200 µg/L	
AZ	Drinking water	200 µg/L	
	Fish consumption	160,000 µg/L	
	Full body contact	13,000 µg/L	
	Partial body contact	13,000 µg/L	
CA	30-day average	540 mg/L	
	- maximum	0.200 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
STATE (Cont.)			
CT	Drinking water	2.0 µg/L	
DE	Freshwater fish consumption	200 mg/L	
	Freshwater fish and water consumption	200 mg/L	
	Marine/estuarine fish/shellfish consumption	28 mg/L	
	Drinking water	0.20 mg/L	
FL	Drinking water	02.mg/L	
GA	Drinking water	0.2 mg/L	
HI	Fish consumption	340,000 µg/L	
IA	Drinking water	0.20 mg/L	
ID	Drinking water	0.20 mg/L	
IL	Drinking water	0.20 mg/L	
IN	Outside of mixing zone (4-day avg.)	1,030,000 µg/L	
	Point of water intake	18,400 µg/L	
KY	Fish consumption	1,030,000 µg/L	
	Domestic water supply source	18.4 mg/L	
LA	Drinking water	200 µg/L	
	Non-drinking water	31.34 mg/L	
MA	Drinking water	0.20 mg/L	
MN	Drinking water	0.20 mg/L	
MO	Drinking water	0.20 mg/L	
	Drinking water supply	200 µg/L	
MT	Drinking water	0.20 mg/L	
NC	Drinking water	020 mg/L	
ND	Drinking water	0.20 mg/L	
NE	Maximum contaminant levels	0.2 mg/L	
NM	Drinking water	0.20 mg/L	
OH	Drinking water	0.20 mg/L	
	Outside mixing zone (max.)	2,000 µg/L	
	30-day avg.	88 µg/L	
	Human Health (30-day avg.)	1,030,000 µg/L	
	Inside mixing zone (max.)	3,900 µg/L	
OK	Drinking water	0.20 mg/L	
OR	Fish and water consumption	18.4 mg/L	
	Fish consumption	1.03 g/L	
PR	Drinking water	0.20 mg/L	
RI	Drinking water	0.20 mg/L	
SC	Drinking water	0.20 mg/L	
SD	Domestic water	200 µg/L	
	All other uses	1,030,000 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
STATE (Cont.)			
TN	Domestic raw water supply	200 µg/L	
TX	Drinking water	200 µg/L	
UT	Drinking water	0.2 mg/L	
VA	Drinking water	0.2 mg/L	
VT	Class A or B waters	18.4 mg/L	
	Class C waters	1.03 g/L	
WI	Drinking water	0.20 mg/L	
	Maximum contaminant levels	0.2 mg/L	
	Public water supplies:	0.2 mg/L	
	- warm water sport fish communities	0.2 mg/L	
	- coldwater communities	0.2 mg/L	
	- Great Lakes communities	0.2 mg/L	
	Non-public water supplies:		
	- warm water sport fish communities	33 mg/L	
	- cold water sport fish communities	11 mg/L	
	- Great Lakes communities	200 mg/L	
WV	Drinking water	0.20 mg/L	
	Water Quality Criteria: Aquatic Life		CELDs 1994
AZ	Acute - cold water fishery	2,600 µg/L	
	Acute - warm water fishery	2,600 µg/L	
	Acute - effluent dominated water	2,600 µg/L	
	Chronic - cold water fishery	1,600 µg/L	
	Chronic - warm water fishery	1,600 µg/L	
	Chronic - effluent dominated water	1,600 µg/L	
HI	Acute - freshwater	6,000 µg/L	
	Acute - saltwater	10,400 µg/L	
LA	Acute - freshwater	5,280 µg/L	
	Acute - marine	3,120 µg/L	
	Chronic - freshwater	2,640 µg/L	
	Chronic - marine	1,560 µg/L	
NJ	Freshwater	18,000 µg/L	
	Saltwater	31,200 µg/L	
OH	Outside mixing zone, maximum	2,000 µg/L	
	Outside mixing zone, 30-day avg.	88 µg/L	
	Outside mixing zone, human health	1,030,000 µg/L	
	Inside mixing zone	3,900 µg/L	
OR	Acute - marine	312,000 µg/L	
	Water Quality Criteria: Recreational Uses		CELDs 1994
TN		170,000 µg/L	
	Groundwater Quality Standards		CELDs 1994
AZ		0.2 mg/L	
CO		200 µg/L	
MO		200 µg/L	

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
STATE (Cont.)			
NC		0.2 mg/L	
NM		0.06 mg/L	
OK		0.3 mg/L	
OR		0.2 mg/L	
UT		0.2 mg/L	
WI	Enforcement Standard Preventive Action	200 µg/L 40 µg/L	
	Groundwater Quality Monitoring Parameters		CELDs 1994
AL		Yes	
CO		Yes	
IL		Yes	
KY		Yes	
LA		Yes	
MN		Yes	
NY		Yes	
SC		Yes	
TN		Yes	
TX		Yes	
VA		Yes	
WI		Yes	
WV		Yes	
	Discharge Limits		CELDs 1994
NJ	NPDES permits: testing requirements for organic toxic pollutant	Yes	
SD	Surface water discharge permit application requirements: Test requirements for organic toxic pollutants	Yes	
WI	Maximum allowable concentration = BAT effluent	Yes	
c. Other			CELDs 1994
	Hazardous Waste Toxicity Characteristics		
TX	Maximum Leachable Concentration	300 mg/L	
	Hazardous Waste Constituents		CELDs 1994
AL		Yes	
CA		Yes	
CO		Yes	

TABLE 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane (continued)

Agency	Description	Information	References
STATE (Cont.)			
GA		Yes	
IL		Yes	
KY		Yes	
LA		Yes	
MA		Yes	
MD		Yes	
MN		Yes	
MT		Yes	
ND		Yes	
NE		Yes	
NH		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
SD		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	

[a]Group 3: Not classifiable as to carcinogenicity in humans.
[b]The current Status of Pesticides in Reregistration and Special Review, March 1992 declares reregistration of products containing methyl chloroform is unsupported.
[c]Group D: Not classifiable as to carcinogenicity in humans.

ACGIH = American Conference of Governmental Industrial Hygienists; BAT = Best Available Technology; BEI = Biological Exposure Index; EPA = Environmental Protection Agency; GC/MS = Gas Chromatogram/Mass Spectrometry; IARC = International Agency for Research on Cancer; LDR = Land Disposal Restrictions; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OGWDW = Office of Groundwater and Drinking Water; OPP = Office of Pesticides Program; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Level; PIC = Products of Incomplete Combustion; REL = Recommended Exposure Level; SIP = State Implementation Plan; SNARL = Suggested No Adverse Response Level; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average; ww = wastewater; nonww = non-wastewater

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{OC})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory- A n estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity- T h e occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo-Occurring within the living organism.

Lethal Concentratlon$_{(LO)}$ (LC_{LO}) The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentratloq$_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{OW})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an Shour shift.

9. GLOSSARY

q_1 *-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. .The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

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(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-l

LSE figures graphically illustrate the data presentedin the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Kev to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

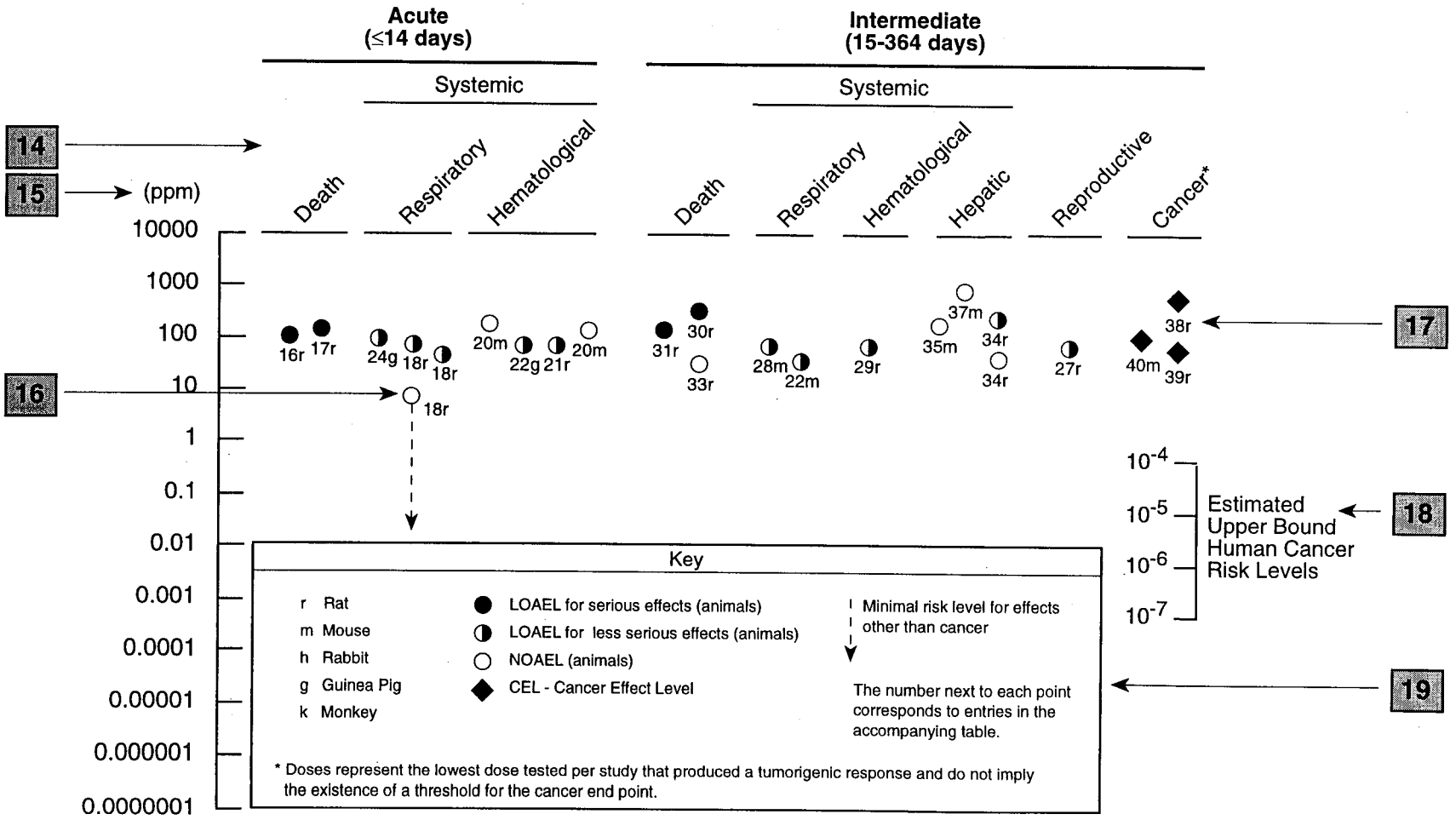
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



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Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (IF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

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